ARCHIVES OF OPHTHALMOLOGY

VOLUME 25 (old series Volume 82) FEBRUARY 1941 NUMBER 2

COPYRIGHT, 1941, BY THE AMERICAN MEDICAL ASSOCIATION

RESULTS FOLLOWING THE TRANSCRANIAL OPERATIVE ATTACK ON ORBITAL TUMORS

WALTER E. DANDY, M.D.

BALTIMORE

Two excellent papers on the pathologic aspects of intraorbital tumors by Byers [1] (1901) and Hudson [2] (1912) emphasized the high percentage of these growths that passed into the cranial chamber. Removal of such a tumor by one of the usual orbital operations, therefore, meant that the patient ordinarily succumbed later to the intracranial growth that remained, and in addition there was local recurrence in the orbit. In 1921 I [3] encountered by the cranial route an intracranial tumor that had extended through the optic foramen into the orbital cavity. The orbital roof was removed in order to follow and extirpate this portion of the tumor. So simple was the operative attack and so perfectly could the intraorbital contents be exposed that this method suggested great improvement in operative attack on the great group of intraorbital tumors. No matter in which direction the intracranial portion of the tumor extends or in which part of the orbit the tumor is situated, this approach has proved far superior to the usual frontal or lateral (Krönlein) routes by which such tumors had previously been attacked. This paper presents the results that have followed the use of this operative approach. And even for the tumors that are confined to the orbit alone, this approach has been found to be preferable to those formerly used by ophthalmologists. The great advantage of this approach lies in the much

Read before the Section on Ophthalmology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. Byers, W. G. M.: Primary Intradural Tumors of the Optic Nerve, Stud. Roy. Victoria Hosp., Montreal **1**:3-82, 1901.

2. Hudson, A. C.: Primary Tumours of the Optic Nerve, Roy. London Ophth. Hosp. Rep. **18**:317, 1910-1912.

3. Dandy, W. E.: Prechiasmal Intracranial Tumors of the Optic Nerves, Am. J. Ophth. **5**:1, 1922; Prechiasmal Tumors Along the Optic Nerves, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 662.

fuller and safer exposure of the intraorbital contents. The optic nerve, the eyeball, three of the extraocular muscles and the ophthalmic veins and arteries can well be exposed and avoided during the dissection of the orbital tumor.

Since the original publication, the operative approach (fig. 1), which is identical with that used for hypophysial tumors, has been greatly reduced and simplified, owing in large part to the introduction of avertin

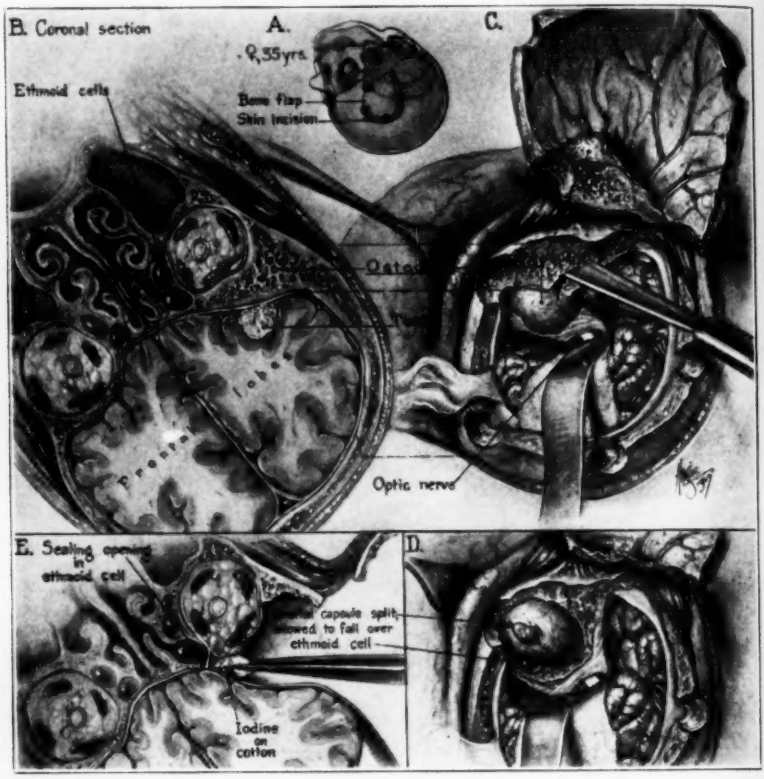


Fig. 1.—Steps in the operative procedure for removal of an orbital tumor by the transcranial route. This particular tumor was one of the intracranial and intraorbital dural meningiomas with marked hyperostosis of the skull and of the orbit.

with amylene hydrate as an anesthetic. It has been found that swelling of the brain that so commonly follows ether anesthesia is avoided when avertin with amylene hydrate is used, and for that reason the size of the bone flap necessary for the exposure of the base of the brain can be greatly modified.

From the clinical examination of patients with exophthalmos it is not usually possible to tell whether or not there is an intracranial extension of the orbital tumor. And all too frequently the orbital tumor is but a small fraction of the large but silent intracranial tumor which is usually the primary growth. Since intracranial tumors are present in approximately three fourths of the orbital tumors in this series, it should be assumed on the law of probabilities that the tumor extends into the cranial chamber. And anything less than the combined transcranial and intraorbital surgical approach will offer no solution of the problem. All too frequently the orbital contents have been exenterated in a radical attempt to remove the tumor from the front of the orbit, and an infected granulating wound has resulted. Such a result would forever preclude the transcranial approach, because of the certainty that infection would follow. In safe hands the transcranial approach carries very little risk, and it offers the maximum hope of cure, unless the frontal bone is involved, and without cosmetic defects. Even when the character of the tumor prevents a permanent cure, the maximum period of relief and extension of life is afforded by subtotal removal of the extensive tumor.

Although the best available evidence of an intracranial component of the tumor is obtained from the roentgenograms, this proof is all too frequently lacking. The optic foramen is occasionally enlarged or reduced in size, but the vast majority of tumors are not continuous through this opening. The dural tumors, which comprise almost half of the tumors in the series, usually but not always show diffuse hyperostosis of the walls of the skull and of the orbit. In cases in which this condition is present there is usually no gross defect in the orbital roof and the extension of the tumor is due to diffuse invasion of the bone. At times calcification may be detected in the intracranial part of the tumor, entirely unsuspected from the clinical data, or a bony prominence may indicate an underlying growth. In none of the cases has enlargement of the sphenoid fissure indicated intracranial participation in the tumor.

TYPES OF GROWTH STUDIED

The data on 24 patients with surgically treated orbital tumors and combined orbital and intracranial tumors are included in this report; in addition, data on 7 other patients who have come to necropsy and have not been subjected to this operation are included for the sake of pathologic study of combined orbital and intracranial tumors. The case reports and operative results in this group will be reserved for a later and more comprehensive paper on this subject. From symptoms alone intracranial extension of the tumor would have been suspected in perhaps 2 patients; in 1 there was headache but no papilledema, and in another there were uncinate attacks.

The character, number and percentage of tumors in the entire series of 31 cases may be summarized as follows:

Type of Growth	No. of Cases	Percentage
Inflammatory mass	1	3.2
Pure fibroma	1	3.2
Pure osteoma (diffuse)	2	6.4
Osteomatous cyst	1	3.2
Spindle cell sarcoma	1	3.2
Round cell sarcoma	1	3.2
Schüller-Christian disease (probable)	5	16
Dural meningioma of nerve sheath (bilateral)	1	3.2
Dural tumors without hyperostosis of the skull (by roentgen examination)	2	6.4
Sarcoma with tremendous hyperostosis of the skull	1	3.2
Dural meningioma with hyperostosis of the skull	11	36
Periosteal sarcoma	1	3.2
Carcinoma	1	3.2

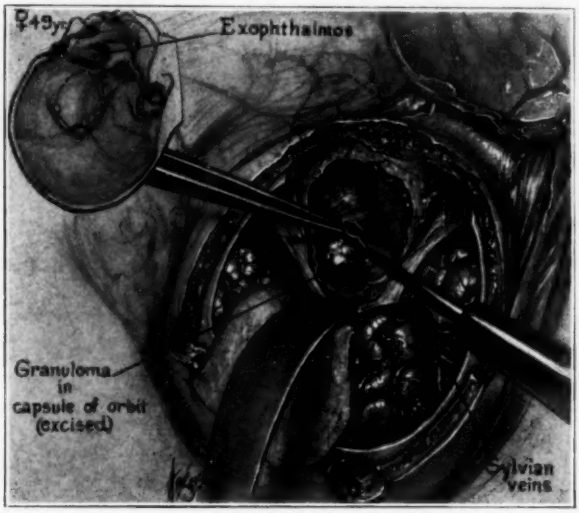


Fig. 2.—Small inflammatory nodule in the orbital capsule. The patient was cured three and one-half years later.

Inflammatory Nodule.—An example of this type of tumor is that in case 1 (fig. 2). The patient is well at the time of writing, three and one-half years later. The proximity of the paranasal sinuses would suggest a much greater frequency of lesions of this type. Doubtless this is true, for it must be in the exceptional case that a persisting mass would form. Most infections would doubtless subside completely spontaneously or after evacuation of an orbital abscess. There was nothing in the histologic picture of this small mass to suggest tuberculosis or syphilis, and the subsequent history of freedom from progression over three and one-half years would be ample evidence against them.

Pure Fibroma.—The origin of the remarkable tumor in case 2 is not entirely clear (fig. 3). It most probably arose from the inferior surface

of the dura to which it was so tightly grown that the dura had to be excised with the growth. Moreover, judging by its intracranial position, where its habitat must have been for many years before it broke through the roof of the orbit and the cribriform plate, its dural origin would appear even more probable. But it is unlike any of the other dural meningiomas in that it contains so few cells. The patient is apparently

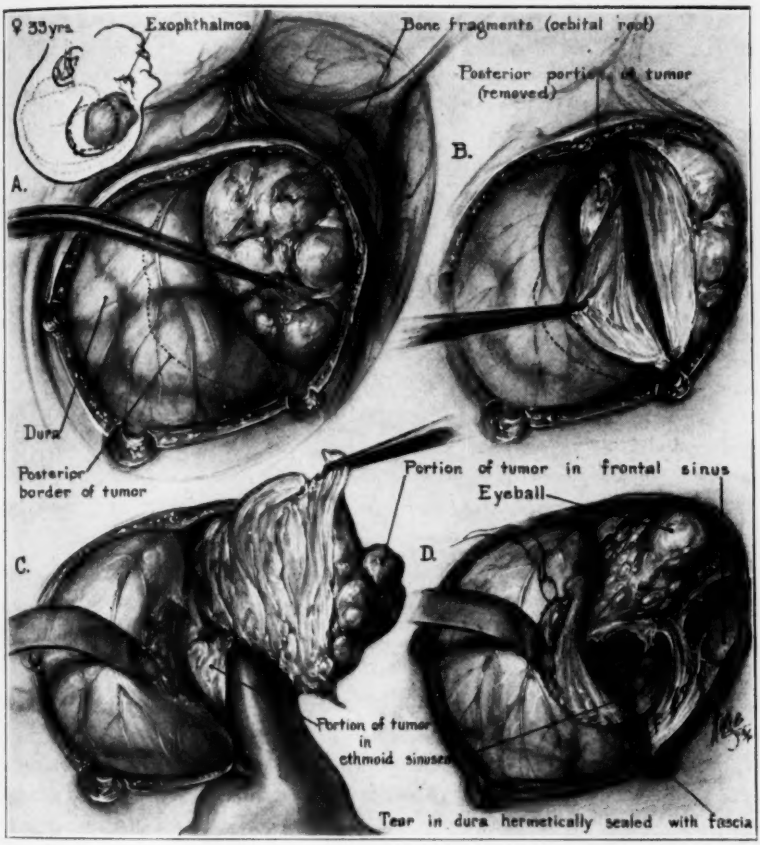


Fig. 3.—Large extradural fibroma filling the frontal region and the orbit. The patient was cured four years later.

well four years later. Stokes and Bowers [4] reported a pure fibroma of the orbit; it was made up of whorls of fibrous tissue.

Pure Osteoma.—By pure osteoma is meant a growth of bone that is not due to a soft tissue-invasive tumor that causes hypertrophy of the

4. Stokes, W. H., and Bowers, W. F.: Pure Fibroma of the Orbit: Report of Case and Review of Literature, Arch. Ophth. **11**:279 (Feb.) 1934.

bone. The latter type of growth occurs with such relative frequency in this series that a degree of skepticism is justified when the diagnosis of pure osteoma is made. One patient (the first reported in this paper but not included in the series of those operated on) has been followed for twenty-one years and is known to have had the growth for forty-three years (since the age of 6 years). The tumor was fully exposed intracranially, as well as intraorbitally, and no sign of an additional soft tumor was found. Moreover, the duration of the tumor's life, with almost no progression in twenty-one years, would appear to exclude safely the possibility of an additional soft tumor. The second patient (case 4) has been followed only two years. It is possible to say only that no soft tumor was found when the entire roof of the orbit was removed. The roentgenologic picture of a pure osteoma differs but little from that of the larger group of secondary soft tumors. Perhaps in these 2 cases the growth invaded the paranasal sinuses to a greater extent, but the involvement of the roof and side of the orbit and of the walls of the skull appears to be precisely similar. The bony growth is diffuse in both cases and its complete removal therefore impossible. It can only be hoped that the results in the second case will be like those in the first.

Well defined localized pure osteomas also occur but have not been encountered in this series. So frequently associated with the frontal or ethmoid sinuses and breaking into the orbit, they have been grouped by Cushing [5] under orbitoethmoid osteomas. Another case has been reported by Pilcher.[6]

Osteomatous Cyst.—In case 4 an unusual tumor arose in or below the floor of the orbit and projected upward into the orbit. The cyst, with serous fluid, was perhaps as large as a bantam's egg. Lining the exposed part of the cyst wall was a thin layer of tumor tissue. Microscopically the lining of the tumor was made up of cellular connective tissue throughout which were thickly interspersed small roughly spherical and irregularly shaped masses of bone. There were numerous osteoblasts and large multinuclear osteoclasts. In most of the bony deposits were osteocytes. The newly formed bone had none of the arrangements of true bone.

Spindle Cell Sarcoma.—It is worthy of note that the tumor in case 5 was removed by intracapsular enucleation, a procedure that would favor local implantation at the site of removal, and yet four years later the patient is well and there has been no recurrence (fig. 4). At the time of the operation the tumor was thought to be malignant, and the lapse of time without recurrence has been a pleasant surprise, the more so

5. Cushing, H.: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, Surg., Gynec. & Obst. **44**:721, 1927.

6. Pilcher, C.: Bony Intracranial Tumors, South. M. J. **31**:613, 1938.

because the patient's other eye had been removed several years previously, after an accident.

Round Cell Sarcoma.—There was a single case of a pure round cell sarcoma (case 6), in a child 2½ years old. Symptoms rapidly developed, and after removal of the growth recurrence quickly followed. In the contiguous region several metastatic or transplanted nodules appeared a few weeks after the operation. This tumor was much the most malignant one in the entire series, death occurring five and one-half months after the first sign of exophthalmos.

Schüller-Christian Disease.—Case 7 furnishes a clinical example of a nodule of this type, which so characteristically perforates the bone. Histologically there were seen numerous masses of foam cells and diffuse infiltration with eosinophils and small round cells, both in great

Fig. 4.—Patient before and after operation for removal of spindle cell sarcoma. He was blind in this eye before the operation. The vision returned promptly and completely. The other eye had been removed in childhood. He was perfectly well four years later.

abundance. The duration of life cannot be told, because the operation was recently performed.

In the 4 remaining cases (8, 9, 10 and 11) the clinical and the gross pathologic appearances were entirely dissimilar. The neoplasm in case 8 behaved like any slowly growing malignant tumor, with local recurrence and localized tumor implants about the site of operation. The gross appearance of the mass was like that of a hard, slowly growing, invasive tumor. The patient is still alive six and three-fourths years after the first symptoms. In none of the sections obtained at two operations were there tumor cells. Because of the foam cells and eosinophils and considering the microscopic, gross and clinical pictures as a whole, Dr. Rich looked on the diagnosis of Schüller-Christian disease as the most probable one.

The growth in case 9 was very rapid (total duration of symptoms until death was ten months) in both orbits, within the cranial chamber and scattered throughout the body. The tumors were salmon colored. From the gross appearance, Dr. Roger Baker, of Duke University, made a diagnosis of xanthomatosis. From the microscopic study of the various masses removed at operation, Dr. Rich stated the opinion that the diagnosis lay between a xanthofibroma and Schüller-Christian disease. No tumor cells were present.

The tumors in cases 10 and 11 were similar in their gross appearance. They were single masses of tissue that grossly resembled hard tumors. Both were firmly fixed, one at the apex of the orbit and the other to the orbital capsule; both had invaded the extraocular muscles, and in both, although the mass could be extirpated, it was clear that the contiguous tissues were infiltrated and that the removal was incomplete. In neither of these, nor in the 2 preceding cases, were there perforations of the cranial vault, which are so typical of Schüller-Christian disease. Only in case 7 was this bony perforation present. This diagnosis in the remaining 4 cases has therefore been made solely on the histologic picture, which more closely resembles Schüller-Christian disease than any other known lesion.

Many cases of Schüller-Christian disease affecting the orbit have been reported, some as instances of xanthomatosis and others of lipoid granulomatosis; and since the condition is not an actual tumor, in many cases it has been classified as a pseudotumor, a designation proposed by Birch-Hirschfeld.[7] Examples of the foregoing reports are those of Ringel,[8] Rowland,[9] Chester,[10] Chiari,[11] Heath,[12] Knapp,[13] and Sautter.[14] Among 70 primary orbital tumors Schreck[15] included 12 as pseudo-

7. Birch-Hirschfeld, A., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 3, p. 78.

8. Ringel, T.: Ueber Tumoren, Pseudotumoren und Fremdkörper der Orbita, Beitr. z. klin. Chir. **126**:239, 1922.

9. Rowland, R. S.: Xanthomatosis and Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928; The Christian Syndrome and Lipoid Cell Hyperostosis of the Reticulo-Endothelial System, Ann. Int. Med. **2**:1277, 1929.

10. Chester, W.: Ueber lipoid Granulomatose, Virchows Arch. f. path. Anat. **279**:561, 1930.

11. Chiari, H.: Die generalisierte Xanthomatose vom Typus Schüller-Christian, Ergebn. d. allg. Path. u. path. Anat. **24**:396, 1931.

12. Heath, P.: Ocular Lipoid Histiocytosis and Allied Phenomena, Arch. Ophth. **10**:342 (Sept.) 1933.

13. Knapp, A.: Xanthomatosis of the Orbit: Report of Two Cases, Arch. Ophth. **11**:141 (Jan.) 1934.

14. Sautter, H.: Beitrag zur Kapitel der entzündlichen Pseudotumoren der Orbita am Hand Klin. Monatsbl. f. Augenh. **100**:29, 1938.

15. Schreck, E.: Zur Klinik und pathologischen Anatomie der Orbitaltumoren, Klin. Monatsbl. f. Augenh. **103**:1, 1939.

tumors, a proportion of non-neoplastic masses not greatly different from those in this series. Six of them were reported to be chronic inflammatory tissue, a diagnosis that could easily have been made in 2 of my cases of Schüller-Christian disease that only Dr. Rich's expert eye would have placed in this group. In 2 of Schreck's 12 cases the diagnoses were lymphogranuloma and aleukemic lymphadenoma. As Schreck did not mention Schüller-Christian disease in his cases, one is led to wonder if the condition in many of them may not have been of this origin.

Voelkel [16] collected 40 cases of bilateral symmetric orbital growths, most of which he thought to be of lymphomatous origin. Doubtless in some of these cases the condition was similar to that in my case 9.

Psammoma (Dural Tumor of the Optic Sheath).—Almost identical tumors were present in both optic nerves in case 12. The point of origin of the growths was from the dura in the optic canal, from which point each projected slightly intracranially and much more intraorbitally. On the side operated on the tumor strangulated the optic nerve like a tight constricting band. Microscopically the tumor was made up of fibrous tissue and was loaded with psammoma bodies. Although the vision was not improved by the operation, the patient is still alive and well except for blindness twenty-four years after the onset of symptoms. Olivecrona and Urban [17] (1935) reported an almost identical case, in which the condition was also bilateral. Schott [18] (1877) reported bilateral symmetric bodies of psammoma of the optic nerves at the optic foramen, but they were more circumscribed than in my case.

Dural Tumors Without Roentgenologic Evidence of Hyperostosis of the Skull and of the Orbit.—The qualification of roentgenologic evidence is added because it is exceptional in this series (cases 14 and 15) for a dural tumor to be unassociated with hyperostosis (fig. 5). As a matter of fact, definite thickening of the sphenoid ridge was seen at operation in both cases, although it was not demonstrable in the roentgenograms either before operation or on subsequent restudy. The highly malignant tumor in case 14 showed only occasionally the arrangement of cells so characteristic of a cellular dural meningioma. Had one not known its character from the gross picture, a diagnosis of sarcoma might well have been made. The duration of life was two years after the first symptoms. After the operation transplanted nodules developed about the operative site.

---

16. Voelkel, R.: Zur Frage der symmetrischen Orbitaltumoren, Klin. Monatsbl. f. Augenh. **98**:169, 1937.

17. Olivercrona, H., and Urban, H.: Ueber Meningeome der Siebbeinplatte, Beitr. z. klin. Chir. **161**:224, 1935.

18. Schott: On Some Affections of the Optic Nerves, Arch. Ophth. & Otol. **6**: 262, 1877.

The tumor in case 15 was like others of the cellular type of dural growths. The cells in most part were grouped in round or oval columns of varying size throughout the sections. The same columns of cells were found in the marrow spaces of the bone. Histologically this growth was similar to the tumors with hyperostosis, to be described.

Tumors With Roentgenographic Evidence of Hyperostosis of the Skull and of the Orbit.—Nine tumors, or over one third of the surgically removed tumors in this series, were associated with such pronounced

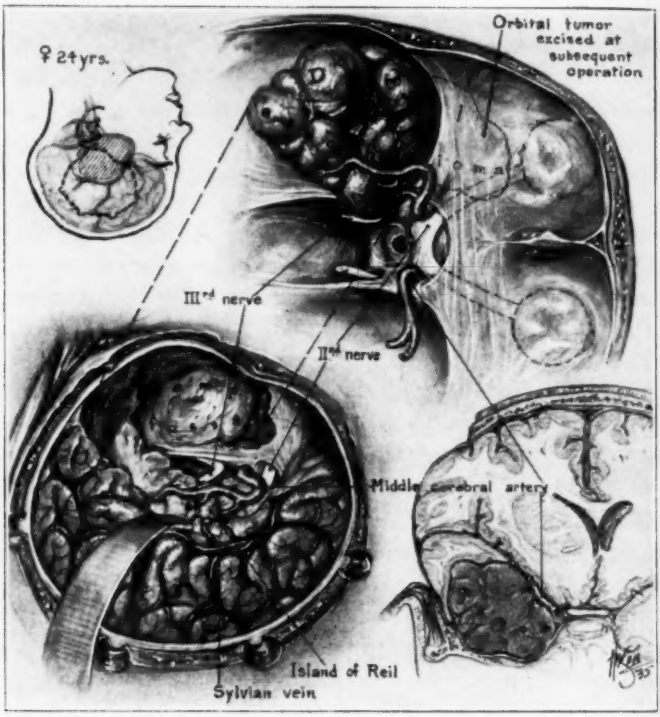


Fig. 5.—Large dural meningioma occupying the middle fossa of the skull and projecting through the sphenoid fissure into the orbit.

hypertrophy of the skull and walls of the orbit that it was strikingly shown in the roentgenograms (figs. 6 and 7). The cause of this relation, recognized by Spiller [19] in 1899 and by Brissaud and Lereboullet,[20] in 1903, was probably first demonstrated by Cushing [21] in 1922. Under

19. Spiller, W. S.: Hemicraniosis and Cure of Brain Tumor by Operation, J. A. M. A. **49**:2059 (Dec. 21) 1907.

20. Brissaud and Lereboullet, P.: Deux cas d'hémicraniose, Rev. neurol. **11**:537, 1903.

21. Cushing, H.: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:139 (Aug.) 1922.

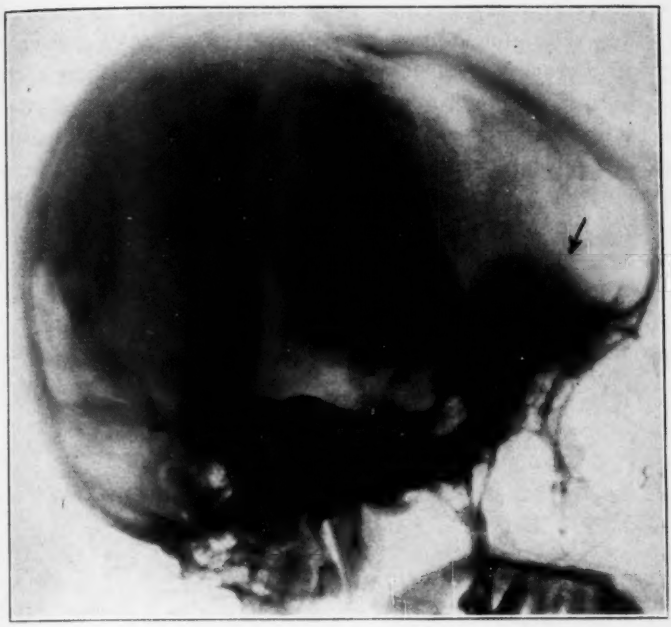


Fig. 6.—Typical roentgenogram in case of dural meningioma with hyperostosis.

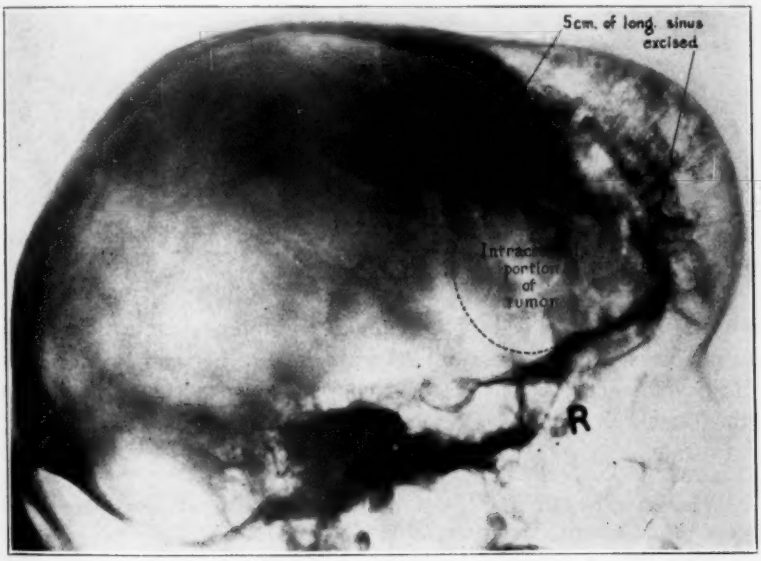


Fig. 7.—Roentgenogram of tremendous bilateral frontal dural meningioma with hyperostosis. The tumor had broken through the roof of the orbit and produced exophthalmos (see fig. 9).

the microscope he found the marrow spaces in the bone to be filled with tumor cells (dural meningioma in each instance). Phemister,[22] Penfield[23] and Bérard and Dunet[24] quickly verified Cushing's findings. This same combination of a dural tumor and superimposed thickening of bone occurs not only with orbital growths but also with those located along all parts of the vault and base of the skull, and always there is the same explanation: The cells of the dural tumor have invaded the overlying part of the skull (fig. 8). That the hyperostosis is not absolutely, although nearly, pathognomonic of a dural meningioma is shown by the same extensive bony proliferation in a case of a sarcoma (spindle cell);

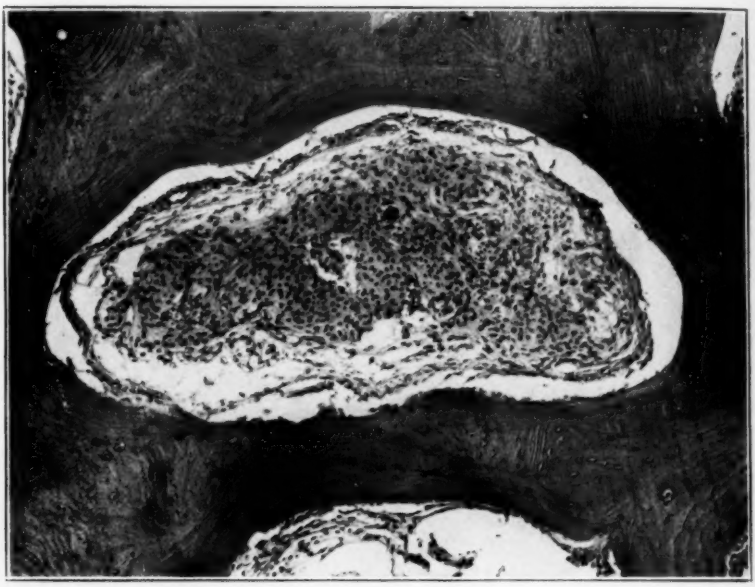


Fig. 8.—Island of dural tumor in the haversian canals of the orbital roof. This is the cause of the hyperostosis in such tumors.

the same sarcomatous cells that made an enormous soft tumor also filled the marrow spaces of the skull. Doubtless the bony change is similar in its development to that of the well recognized areas of hypertrophy of the vertebral column associated with metastases from carcinoma of the prostate.

---

22. Phemister, D. H.: The Nature of Cranial Hyperostosis Overlying Endothelioma of the Meninges, Arch. Surg. **6**:554 (March) 1923.

23. Penfield, W.: Cranial and Intracranial Endotheliomata Hemicraniosis, Surg., Gynec. & Obst. **36**:657, 1923.

24. Bérard, L., and Dunet, C.: Hypérostoses crâniennes et tumeurs méningées, Lyon chir. **21**:502, 1924.

The roentgenograms of the benign osteomas in this region and elsewhere presented no demonstrable difference from those of the invasive meningeal growths. Doubtless the age of the patient is an important differential point, for in both of the benign hyperostoses the bony thickening was present in the first decade. And none of the dural tumors was known to be present before the thirtieth year. Although benign osteoma may well appear later, the burden of proof must be on the acceptance of such a diagnosis after this age.

The size, position and general character of the dural tumor in relation to the size of the hyperostosis of the orbit and of the skull is worthy of consideration. The dural growth in case 16 is especially interesting because there was no dural meningioma on the side of the dura contiguous to the hyperostosis. It was only because the dura was opened that it was seen at all; and then it was only a flat plaque, about the thickness of paper and very loosely applied to the cerebral side of the dura. It gave no gross appearance of having infiltrated the dura and was stripped from the dura with the greatest ease. Sections of the bone, which was tremendously thickened, showed the same type of tumor. In 2 other cases (17 and 22, the latter studied at necropsy) there was no gross dural tumor; but in the orbital fat of each there was a small diffuse irregular mass looking like firm granulation tissue, and this proved to be tumor. From the gross appearance one would be led to wonder if this orbital tumor might not have been a secondary outgrowth from the tumor within the bone. Could this dural tumor have arisen from dural rests within the bone which in each instance was of enormous size? In case 22 the hyperostosis was the most extensive of the entire series. In case 23 the dural growth was hard and flat, about 1 cm. thick and spread like a carpet over the entire orbital roof, to which it was firmly attached; it extended posteriorly, covering the dura over two thirds of the floor of the middle fossa; the hyperostosis was of moderate grade. In case 19 the dural tumor arising from the orbital roof was about the size of a hazelnut. In case 20 a hazelnut-sized dural tumor projected from the sphenoid wing. In case 21 a small (2 cm. in diameter) round dural tumor projected intracranially from the orbital roof, and the irregular mass of grayish brown tissue like granulation tissue projected into the posterior part of the orbit.

On the other hand, the dural tumor in case 18 was of great size and very hard (fig. 9). In this case the orbital roof was destroyed and the hyperostosis was confined to both frontal bones.

Viewed histologically, with a single exception (case 18), the tumors were all of the very cellular type of meningioma and were lacking in the whorls and palisades of fibrous tissue. In case 18, however, the tumor was made up of whorls and palisades and was lacking in the solid masses

of cells. Both types of dural tumor can, therefore, be responsible for the extensive contiguous hyperostosis. Moreover, the degree of hyperostosis is just as great with small circumscribed or thick carpet-like tumors as with the larger growths. Cushing and Eisenhardt [25] commented on the fact that a greater proportion of dural tumors "en plaque" produced hyperostosis than those of the large, hard, rounded tumors, which he termed the "global type." However, the same change in the bone is produced by both types. Surprising indeed is the extensive and widespread distribution of the hyperostosis which so frequently involves much of the orbital bones, the side and front of the skull and all too frequently the paranasal sinuses. So much are the paranasal sinuses

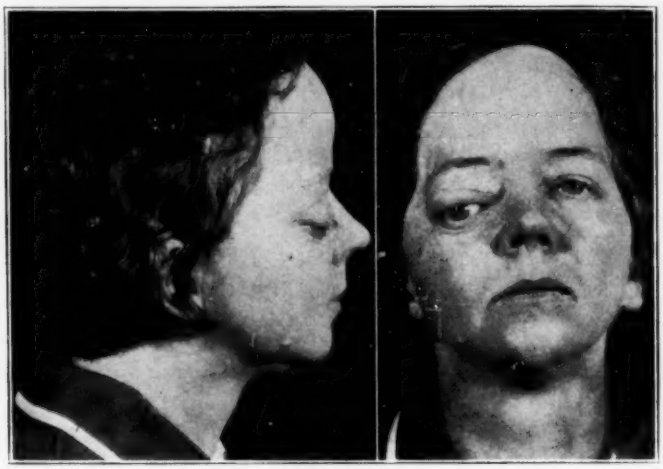


Fig. 9.—Patient with bilateral frontal dural meningioma (see fig. 7).

involved that these growths have been included by Cushing under "orbitoethmoid" tumors.

Operative removal of tumors of this type has been reported by Cushing,[21] Armitage,[26] Patterson and Cairns,[27] Vorhis and Adson,[28] Love,[29] Hoover and Horrax,[30] Vincent and Mahoudeau,[31] Pilcher [6] and

25. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

26. Armitage, A.: Osteoma of Frontal Sinus with Intracranial Complications, Brit. J. Surg. **18**:565, 1931.

27. Patterson, H., and Cairns, H.: Observations on the Treatment of Orbital Osteoma, with Report of a Case, Brit. J. Ophth. **15**:458, 1931.

28. Vorhis, H. C., and Adson, A. W.: Meningiomas of the Sphenoidal Ridge with Unilateral Exophthalmos, S. Clin. North America **14**:663, 1934.

29. Love, J. G.: Transcranial Removal of an Intraorbital Meningioma, Proc. Staff Meet., Mayo Clin. **10**:213, 1935.

Cairns.[32] Knapp [33] reported 2 cases, in 1 of which an operation was performed and in the other of which roentgen therapy was given. Elsberg, Hare and Dyke [34] reported 5 cases of tumors of this type, in some of which the dural growth was removed, but apparently without removal of the orbital hyperostosis.

Glioma of the Optic Tracts.—Four cases are added for pathologic study; in all exploratory operations were performed, but in none did the operation include the orbital attack, the tumor being clearly inoperable. In 2 of the cases there was no exophthalmos despite the fact that the growth had continued into the orbit. All the growths were widespread, involving the chiasm and one or both optic nerves within the cranial chamber and also in the orbits, and in each the brain was also involved. In one instance the tumor extended through the third ventricle and the temporal, frontal, parietal and occipital lobes on one side. All these tumors were in young children, the ages being 4, 5, 7 and 13 years. This type of tumor may be suspected when hemianopia in the eye without exophthalmos is present or beginning. A case of this type was reported by Willemer [35] as early as 1879; an excellent drawing was included. Other cases have been reported by Martin and Cushing.[36]

Lundberg [37] made an extended study of this tumor, which he classified as an "oligodendrocytoma." He emphasized the early age of onset. Busch [38] suggested partial extirpation of the growth and recorded 2 cases in which there was improvement after two and one-half and seven and one-half years. However, very little operative trauma can be sustained without mortality, because the subsequent edema involves the hypothalamus, which tolerates trauma poorly.

---

30. Hoover, W. B., and Horrax, G.: Osteomas of the Nasal Accessory Sinuses, with Report of a Case Illustrating the Transcranial Approach to Orbital Structures, Surg., Gynec. & Obst. **61**:821, 1935.

31. Vincent, C., and Mahoudeau, D.: Sur un cas d'ostéome ethmoïdo-orbitaire avec pneumatocèle opéré par la méthode de Cushing, Rev. neurol. **68**: 993, 1935.

32. Cairns, H.: Peripheral Ocular Palsies from the Neurosurgical Point of View, Tr. Ophth. Soc. U. Kingdom **58**:464, 1938.

33. Knapp, A.: Orbital Hyperostosis: Its Occurrence in Two Cases of Meningioma of the Skull, Arch. Ophth. **20**:996 (Dec.) 1938.

34. Elsberg, C. A.; Hare, C. C., and Dyke, C. G.: Unilateral Exophthalmos in Intracranial Tumors with Special Reference to Its Occurrence in the Meningiomata, Surg., Gynec. & Obst. **55**:681, 1932.

35. Willemer, W.: Ueber eigentliche d. h. sich innerhalb der äusseren Scheide entwickelnde Tumoren des Sehnerven, Arch. f. Ophth. (pt. 1) **25**:189, 1879.

36. Martin, P., and Cushing, H.: Primary Gliomas of the Chiasm and Optic Nerves in Their Intracranial Portion, Arch. Ophth. **52**:209, 1923.

37. Lundberg, A.: Ueber die primären Tumoren des Sehnerven und der Sehnervenkreuzung, Inaug. Dissert., Stockholm, Nordiska Bokhandeln, 1935.

38. Busch, E.: Surgical Treatment of Gliomas of the Optic Nerve and the Chiasma, Zentralbl. f. Neurochir. **2**:364, 1938.

Other Tumors in the Orbit.—The foregoing pathologic report by no means exhausts the orbital tumors. They merely represent the cases that have occurred in the experience of a neurosurgeon and very probably are fairly representative of the commoner types. Coulter and Coats [39] reported an orbital teratoma and Gow [40] a large cyst that was probably of this character. Mancilla [41] and Byers [42] each reported a cavernous angioma of the orbit; Adson and Benedict,[43] a hemangio-endothelioma, Franklin and Cordes,[44] a lymphangioma; Knapp,[45] an oil cyst lined by epithelial cells and containing many sebaceous glands and a few hair follicles; Wheeler,[46] an orbital cyst with epithelial lining; Stallard,[47] a cavernous angioma; de Schweinitz,[48] a myxosarcoma and a lipoma; Pinkus,[49] 2 cases of cholesteatoma of the orbit, and Cairns,[32] a cholesteatoma arising beneath the orbital roof. Van der Hoeve [50] reported a case of von Recklinghausen's neurofibroma and Steurer [51] 2 other cases of this condition; the latter also included a case of an epidermoid with slight hyperostosis of the orbital roof with 6 cases of dural hyperostosis causing exophthalmos. Davis [52] reported 2 cases of

39. Coulter, R. J., and Coats, G.: Teratoma of the Orbit, Roy. London Ophth. Hosp. Rep. **18**:64, 1910-1912.

40. Gow, W. H.: Orbital Tumor: Report of Unusual Case. Brit. J. Ophth. **18**:520, 1934.

41. Mancilla, G. A.: A Cavernous Angioma of the Orbit, Rev. méd. de Sevilla **42**:26, 1923.

42. Byers, W. G. M.: Case of Encapsulated Angioma of Orbit, Arch. Ophth. **53**:280, 1924.

43. Adson, A. W., and Benedict, W. L.: Hemangio-Endothelioma of the Orbit: Removal Through Transcranial Approach, Arch. Ophth. **12**:484 (Oct.) 1934.

44. Franklin, W. S., and Cordes, F. G.: A Case of Orbital Lymphangioma, J. A. M. A. **83**:1741 (Feb. 16) 1924.

45. Knapp, A.: Oil Cyst of Orbit, Arch. Ophth. **52**:163, 1923.

46. Wheeler, J. M.: Orbital Cyst Without Epithelial Lining: Report of Two Cases of Blood Cyst, Arch. Ophth. **18**:356 (Sept.) 1937.

47. Stallard, H. B.: Cavernous Hemangioma of the Orbit Successfully Removed by Krönlein's Operation, Lancet **1**:131, 1938.

48. de Schweinitz, G. E.: A Contribution to the Subject of Tumors of the Eyelid and Orbit, Tr. Am. Ophth. Soc. **14**:341, 1915.

49. Pinkus, F.: Ueber "Cholesteatoma" der Orbite, Klin. Monatsbl. f. Augenh. **90**:145, 1933.

50. van der Hoeve, J.: Röntgenphotographie des Foramen opticum bei Geschwülsten und Erkrankungen der Sehnerven, Arch. f. Ophth. **115**:355, 1925.

51. Steurer, O.: Ueber Beiteiligung des inneren Ohres und des Hörnerven bei multipler Neurofibromatosis Recklinghausen, mit besonderer Berücksichtigung des sekundär absteigenden Degeneration des Hörnerven, Ztschr. f. Hals-, Nasen- u. Ohrenh. **4**:124, 1922.

52. Davis, F. A.: Plexiform Neurofibromatosis (Recklinghausen's Disease) of Orbit and Globe, with Associated Glioma of Optic Nerve and Brain: Report of Case, Arch. Ophth. **22**:761 (Nov.) 1939.

plexiform neurofibromatosis, in 1 of which the condition was associated with a glioma of the optic nerve. There are doubtless few tumors encountered elsewhere in the body that do not also appear in the orbit.

THE OPERATIVE PROCEDURE

The size of the cranial exposure has been greatly reduced since the earlier report. This is in large part due to the use of avertin with amylene hydrate as the routine anesthetic in operations on the brain. The great operative disadvantage of ether lies in the swelling of the brain that usually follows. It was to make allowance for this that the larger bony exposure was required. With the use of avertin with amylene hydrate the brain does not swell, and therefore a much smaller bony opening will serve just as effectively as the larger one when ether is used.

For exposure of the orbital roof the regular hypophysial approach is made. The concealed incision has for many years been employed in all operations on the brain and with no loss of room or increased difficulty of approach. The cutaneous incision begins about 2 cm. anterior to the ear, passes straight toward the midline and about 3 cm. from it makes a sharp curve forward and ends anteriorly at, or slightly in front of, the hair line. The galea and the skin are then stripped from the bone and temporal muscle and retracted anteriorly.

The bone flap is made so that the anterior border misses the frontal sinus and skirts the supraorbital ridge as far laterally as possible. When turned back and broken under the temporal muscle it is retracted laterally and is well out of the way. The dura is opened just within the bony margin, and the roughly circular incision is so complete that it becomes practically an autotransplant, thus being a factor in preventing postoperative extradural bleeding. The frontal lobe is elevated and the cisterna chiasmatis evacuated, thus reducing the volume of intracranial contents and providing room for attack on the roof of the orbit. The head is then lowered to permit the frontal lobe to fall away without the need of traction.

If the cisterna chiasmatis is not opened, the brain so completely fills the operative field that undue pressure would usually be necessary to retract the frontal lobe to a degree sufficient to permit the attack on the orbit and its contents.

From the optic foramen the dural covering of the orbital roof is incised in a curve, sweeping it laterally around the outer margin of the orbit and then curving anteriorly almost to the cribriform plate. The dural flap is stripped toward the midline with a periosteal elevator.

The initial opening in the orbital roof can frequently be made by applying slight force with the periosteal elevator at the thinnest point of the bone. The remainder of the roof is removed with rongeurs, care

being taken not to extend the defect into the ethmoid cells. In 2 of my cases this happened and rhinorrhea promptly followed, necessitating reopening the wound and covering the opening with bone wax and the flap of dura. At times the bone is so thickened (by an osteoma) that the chisel is necessary to make the primary defect, and it may then be necessary to complete the removal of the roof with numerous applications of this instrument.

The capsule of the orbit then presents and is incised longitudinally and the edges retracted. Either the tumor or orbital fat presents, depending on the position of the growth. If fat presents, the growth is under pressure and extrudes and must be excised. Identification of the superior rectus muscle is usually immediate, unless the tumor is superimposed. This muscle is surrounded by a silk suture and retracted to one side, which provides inspection of the entire superior half of the orbit. From this view a tumor in any part of the orbit will be found, and its extirpation can be carried out deliberately. The optic nerve, the posterior part of the eyeball and the ophthalmic artery and vein are readily identified.

In only 1 case, in which evacuation of the cisterna provided much less room than normal, was there any trauma to the frontal lobe. Rather than take any chance with subsequent postoperative edema and intracranial pressure, a small part of the frontal lobe was removed. In closing, the dura is snugly resutured; the bone flap is replaced and wired, and the galea and the skin are closed without drainage.

There has been but 1 death in the series (case 22). With the huge mass of bone along the base of the middle and the anterior fossa, it doubtless would have been wiser to be content with a partial removal of the growth with the chisel rather than to attempt such an extensive extirpation.

The thought doubtless occurs: Does not pulsating exophthalmos follow removal of the orbital roof? I have looked carefully for such a sequel but have never found it, despite the fact that pulsating exophthalmos is known to occur when the orbital roof is congenitally absent.

Although I have never done a lateral Krönlein operation for an orbital tumor, it does not seem possible that it can provide the exposure for deliberate painstaking dissection of a tumor that is necessary to avoid injury to important structures within the orbit. And for tumors that extend beyond the orbital cavity, the Krönlein operation would, of course, be perfectly futile.

When an orbital tumor is small and protrudes anteriorly beyond the orbital ridge, the attack on the tumor by an incision under the supraorbital ridge is doubtless adequate, but when the tumor extends back of the eyeball the intracranial approach is advisable.

Before the operation is begun, the size and position of the frontal sinuses should be known. In making the anterior bony incision it is important that the frontal sinus be avoided. Entry into a frontal sinus is a potential source of infection and of subsequent rhinorrhea. If a frontal sinus is opened a flap of dura should be tightly sutured over the opening. If an ethmoid cell is opened it can be covered with wax and the dural flap replaced over it. A small opening in the frontal sinus may also be covered with wax, but the larger openings would require a dural flap. In none of the cases in this series was the frontal sinus opened. In case 18 the enormous tumor of long standing had completely obliterated the frontal sinuses, but the paranasal sinuses communicated with the wide open cerebral chamber (the whole frontal dura on both sides was removed with the attached tumor). No attempt was made to close this defect, and neither rhinorrhea nor infection followed. In 2 cases of this series infection followed entry into the ethmoid sinus and the bone flap had to be sacrificed.

The method of attack on the intracranial part of the tumor is dependent on the nature and position of the growth. Usually the hypophysial approach affords ample room. If the middle fossa or temporal lobe contains a large dural growth, it may be necessary to rongeur away an additional area of bone beneath the temporal muscle. This was done in 2 of my cases. It has not been necessary to enlarge the cutaneous incision or to turn down an additional bone flap, either of which, however, is easily possible if the situation should demand. Retraction of the temporal muscle with or without transverse division of its fibers will, after the underlying bone has been removed, expose most of the temporal lobe and even permit its resection in large part if necessary. The removal of a large dural endothelioma is always a difficult feat and requires ample room. Since the arterial bleeding is from the middle meningeal artery, the tributaries of which cover the middle fossa to the foramen spinosum, it is essential that access to this area be unimpeded by inadequate exposure. The dural attachments should, when possible, be totally excised. As long as the dura along the floor of the middle fossa is the site of origin this is not difficult; in fact, the removal of this dura also greatly facilitates control of the severe bleeding from the middle meningeal artery. Not infrequently control of this bleeding is best accomplished by immediately following the middle meningeal artery to the foramen spinosum. Ligation or cauterization of the trunk of this vessel is usually far easier and safer than attempting to control the numerous bleeding points from its many branches.

The problems associated with the intracranial portion of these tumors are those encountered in any series of tumors of the brain. The risk involved in removing combined intraorbital and intracranial growths is confined almost exclusively to the part of the tumor within the cranial

chamber, and the accompanying group of cases shows that even with enormous growths the danger is relatively slight.

Occasionally the internal carotid artery is surrounded by tumor, or at least attached to it. This complication occurred once (case 15) in this series of cases. To injure the internal carotid artery or the middle cerebral artery would mean disaster and must be avoided at all hazards. Rather than invite hemiplegia and probably death from arterial thrombosis by shaving the tumor too closely, there is no choice but deliberately to leave a nest of cells on this vessel.

When there is some exophthalmos and a dural endothelioma has been completely removed from the middle or anterior fossa, should one open the orbit? The answer is dictated by the fact that the bone about the tumor is thickened because of tumor contained within it. In 1 patient with this condition I removed the orbital roof, but since the eye was already blind (case 15) I did not incise the orbital fascia. Since the additional exposure of the orbit is simple and not time consuming and adds practically nothing to the operative risk, the surgical possibilities should be completed in one stage; moreover, a second stage is much more difficult, and the possibilities of a complete cure are reduced.

The most difficult surgical problem with this series of tumors has been in attacking the bilateral frontal tumors of enormous size. This was done in 2 cases. A bilateral approach was made with a long sweeping curve from one ear to the other and just under the hair line. The bone was so thick that the ordinary instruments used for making bone flaps were of little avail. Between large deep burr openings the bone was cut in a curve from the supraorbital ridge on one side to that on the other with large bone-cutting forceps. When the huge bone flap was turned back on the supraorbital ridge, the dura, which was densely attached, tore with it; this included the anterior part of the frontal sinuses, which, however, were practically obliterated by the tumor masses. This bone must, of course, be removed.

In May 1884 a remarkable extirpation of a tumor was performed by Durante,[53] of Rome, perhaps the earliest successful operation of its kind. It antedated by seven months the celebrated case of Rickman Gorlee, of England, to whom is usually accredited the first successful extirpation, although the removal was only partial. Whether or not Lister's aseptic methods were used is not stated in Durante's publication. His patient survived many years and was even apparently cured, the tumor doubtless being a dural endothelioma. The patient happened to be one with exophthalmos secondary to rupture of the orbital roof. A drain was placed from the depths of what Durante thought to be the nasal cavity, from rupture of the ethmoids, but one is led to wonder if on

53. Durante, F.: Contribution to Endocranial Surgery, Lancet **2**:654, 1887.

account of the exophthalmos it might not have been the orbit; no infection followed. Durante's diagnosis was based on the patient's loss of smell, and the case is therefore one of the very earliest ones in which operation was performed after localization of the growth had been made from neurologic signs. The field of cerebral localization, based on the experiments of Fritsch and Hitzig and of Ferrier, was just beginning to stimulate interest and bring results. Except for the facts that the frontal bone was chiseled away and therefore sacrificed and no attempt was made to remove the orbital roof, the operative approach was strikingly similar to that presented in this paper.

In a recent publication on meningiomas (1938), Cushing and Eisenhardt [25] called attention to this approach, which they expected to use in forthcoming cases of tumor of the orbit. Adson and Benedict [48] (1934), Hoover and Horrax [30] (1935) and doubtless others have used this approach to remove orbital tumors.

PROPORTION OF (1) PURELY ORBITAL AND (2) COMBINED ORBITAL AND INTRACRANIAL TUMORS

Of all the tumors included in this report, only 6, or 20 per cent, were confined solely to the orbit, and 1 of these was an inflammatory nodule. The combined incidence of orbital and intracranial tumors was, therefore, 80 per cent. If only the tumors in the operative series of 24 cases are analyzed, 25 per cent would be solely orbital and 75 per cent combined orbital and intracranial. In the entire series (both pathologic and operative observations) it is probable that all of the combined tumors arose primarily in the cranial chamber, except perhaps those which were multiple (in the 4 cases of glioma and the 1 case of Schüller-Christian disease, case 9). The earlier papers of Hudson and of Byers had prepared us for the high percentage of combined orbital and intracranial tumors, but their figures were even lower than our own. They, however, did not have the advantage of direct inspection of both cavities simultaneously but were dependent on necropsies or histories providing unmistakable evidence of subsequent intracranial lesions. If, however, the 23 postmortem examinations of orbital tumors reported in the combined papers of Byers and Hudson with 21 intracranial extensions of the growth are considered, it will be seen that the involvement of both the orbital and the cranial chambers actually exceeds the figures in this report.

MALIGNANCY OF TUMORS IN THIS SERIES

From the series of 24 patients operated on the outcome for only 1 is unknown (case 13). Five are known to be dead of the following causes and after the following intervals: (1) round cell sarcoma, three and one-half months after operation (case 6); (2) Schüller-Christian

disease or xanthoma, five months after operation (case 9); (3) a malignant dural meningioma, twenty-two months after operation (case 14); (4) a dural meningioma with hyperostosis, ten years after operation (case 16), and (5) an operative death (case 22).

In 3 cases at least, and probably more, the condition is benign and should be permanently cured: case 1, an inflammatory nodule, three and one-quarter years; case 2, a fibroma, four years, and case 3, a spindle cell sarcoma, three years.

In the remaining cases the tumors must be looked on as malignant or as benign growths that could not be completely removed. The great group of dural tumors must be considered malignant because the orbital roof and frequently the skull over a large area were invaded by such a neoplasm and its complete extirpation was therefore impossible. The growth of a dural tumor, however, is usually very slow, and there should be relief for many years; one patient (case 16) survived ten years, and all the patients have survived a number of years. The same is doubtless true of the sarcoma with hyperostosis (case 13); this patient's subsequent course cannot be traced, but he was well when he left the hospital. Two other potentially benign tumors could not be completely removed (case 3, an osteoma, and case 12, a bilateral dural psammoma of the optic sheath). In the latter case eighteen years has passed since the operation and the tumor has made no observable progress. It is hoped that the osteoma (case 3), operated on two years ago, will grow as slowly as that in the introductory case in this paper, which has shown no recognizable progress in twenty-one years.

In the 4 living patients with Schüller-Christian disease the condition must be considered malignant. In the case of 1 of them (case 8) nearly three years has passed, but local recurrence is slowly progressive. The other 3 patients (cases 7, 10 and 11) have been operated on in the past few months, and although other lesions cannot be found and the orbital growth has been thoroughly removed, with contiguous tissue, a cure can hardly be expected.

SUMMARY

A series of 24 intraorbital tumors that have been operated on by the transcranial route is reported. Five, or 21 per cent, of these tumors were confined to the orbit; 18, 79 per cent, were combined intraorbital and intracranial growths; 1 of the former and 2 of the latter were metastatic. With an additional 7 cases in which necropsy was performed but this operation had not been employed, the percentages are even more pronounced, 16⅔ per cent and 83⅓ per cent respectively. The pathologic features of the tumors are discussed.

The operative attack, proposed in 1921, is through a transcranial (hypophysial) approach. The roof of the orbit is removed after

evacuating the cisterna chiasmatis; retraction of the frontal lobe then provides sufficient room.

The operation is offered not only for all combined intraorbital and intracranial tumors but for growths that are restricted to the orbital cavity. As a matter of fact, it is rarely possible before operation to be certain whether or not the tumor also lies within the cranial chamber, as so many of them do (roughly 75 to 80 per cent in this series). Their coexistence should therefore be assumed on the law of probability.

For tumors confined to the orbit this operation offers a far better exposure of the tumor than is possible by any other method. Deliberate, careful dissection of the tumor is possible only by this approach. There is therefore much less chance of injury to the extraocular muscles, their nerve supply, the optic nerve and the ophthalmic vessels by this approach.

It offers the only hope of a permanent cure when the tumor is in both cavities, and when the condition is incurable it offers the maximum palliative result.

The operative risk in safe hands should be very low (4.1 per cent in this series) in regard to both tumors confined to the orbit and those with intracranial extensions. Prior exenteration of the orbit or removal of the eyeball will prevent the utilization of this operation, because the orbital tissues will be infected.

ABSTRACT OF DISCUSSION

Dr. Arnold Knapp, New York: In 1886 the eminent Swiss surgeon Krönlein devised the temporary resection of the external bony wall of the orbit and thereby greatly advanced retrobulbar surgery. Dr. Dandy in 1922 proposed an operation for orbital tumors through an intracranial approach. He has just given a report on 23 intraorbital tumors, of which 5 were confined to the orbit and 18 were combined intraorbital and intracranial growths.

He recommends this operation not only for combined intraorbital and intracranial tumors but for tumors restricted to the orbital cavity. He claims that for intraorbital tumors a far better exposure of the tumor is possible by this operation than by any other method, and as it is impossible to be certain before operation that the tumor does not also lie within the cranial cavity, it is necessary to be prepared to deal with the possible intracranial tumor.

Although the logic of the operation for combined tumors is granted, the intracranial operation appears unduly formidable to the ophthalmologist who has seen many orbital tumors adequately treated by simpler operations. The question arises: What kind of orbital tumors is the ophthalmologist usually called on to treat? In looking over my experience of more than forty years, when I have paid particular attention to orbital tumors, aside from the occasional isolated tumors with freak histologic pictures, I find that the usual orbital tumors belonged to the following groups, in order of frequency: angioma, sarcoma, dermoid, osteoma, tumors of the lacrimal gland, chronic inflammatory growths

and tumors of the optic nerve. These tumors were all adequately taken care of, as far as it is possible to do so, by surgical removal, except the tumors of the optic nerve, which are the only ones for which an extension into the cranium must be considered.

In the Jackson Memorial Volume (Contributions to Ophthalmic Science, Dedicated to Dr. Edward Jackson, Menasha, Wis., George Banta Publishing Company, 1926, p. 69) I reported the histories of 3 patients with glioma of the optic nerve who had the tumor removed by the Krönlein operation with preservation of the eyeball. The first of these patients was operated on in 1923, and in 1940 there were no intracranial symptoms; the appearance of the eye on the side of the operation was satisfactory, and the other eye was normal. The second patient was operated on in 1925, and in 1940 the patient was in as good condition as the first one. The third patient was also operated on in 1925, and in 1940 the patient stated that his health was excellent and that his eyes have never given him any trouble. In short, in observation periods of seventeen years in 1 patient and of fifteen years each in 2 patients no evidence of intracranial extension was observed. In these 3 the optic canal was found enlarged on roentgen examination. This corresponds with the well recognized clinical course of these tumors, and it is a hard question to decide whether an extensive intracranial operation should now be recommended in the absence of intracranial symptoms.

Undoubtedly Dr. Dandy has more formidable tumors to deal with than fall in the province of the ophthalmologist. He is to be congratulated on his brilliant results in the treatment of the combined tumors with his intracranial method. As for the tumors restricted to the orbital cavity, I feel convinced that they can be taken care of with simpler and less dangerous procedures.

Dr. William L. Benedict, Rochester, Minn.: When the ophthalmologist is called on to consider cases of unilateral exophthalmos he must first decide whether the exophthalmos is due to a tumor, an inflammation or an invasion of the orbit from without. It is not always simple to make a diagnosis of intraorbital tumor even when it is present, and at times it is still more difficult to determine whether or not, if the tumor has originated in the orbit, it has extended into the cranial cavity or, if it has originated within the cranial cavity, it has extended into the orbit.

By what criteria can the consultant determine the extent of the orbital tumor? One of the best aids is roentgenography. If there are severe changes in the bony walls of the orbit, those changes may be made manifest in the roentgenogram as a hyperostosis or erosion of the walls of the orbit or some deformity. The hyperostosis, or the thickening of the bone, as Dr. Dandy has said, is probably due to invasion of the bone by the tumor, and the tumor that is most usually encountered in such a case is the so-called meningioma. However, vascular tumors that arise within the orbit will produce changes in the bony walls of the orbit that, in so far as the roentgenogram is concerned, are similar to changes found with meningiomas. A pulsating hemangioma, a thrombosed venous aneurysm and a fibrosarcoma within the orbit may produce hyperostosis of the roof of the orbit simulating that of meningioma of the sphenoid ridge.

The hemangiomas usually begin extraorbitally and invade the orbit. It must be remembered, however, that a similar tumor may arise within the orbit and extend intracranially.

There are other tumors, however, that do not give rise to bony changes, and it is sometimes difficult to determine whether or not the cranial cavity has been invaded. If it is evident from palpation of the tumor or from the visual field changes or lack of changes that the tumor may be reached from the anterior approach, there are many methods of attack with which the ophthalmic surgeon is familiar and which, as Dr. Knapp has said, provide adequate means for removal of the tumor without transcranial invasion.

In my experience, tumors confined to the orbit, as compared with those combined intraorbitally and intracranially, do not nearly reach the extent reported by Dr. Dandy. Without having counted the cases, my impression is that less than 25 per cent of the tumors are combined intraorbital and intracranial ones.

I have only one word of warning. I think that the ophthalmic surgeon should never enter the orbit for removal of a tumor unless he feels certain that he can complete the operation at that one sitting. It is dangerous to enter the orbit, find a tumor and then back out and expect another ophthalmologist or a neurosurgeon to finish the job. On the other hand, the hazard of the transcranial approach is not great.

I have some slides showing the results of a transcranial operation for orbital tumor. The method of approach is similar to that described by Dr. Dandy, with probably a larger flap.

The first slide shows the type of tumor, a meningioma that is associated with hyperostosis. This type of so-called osteoma cannot be removed by the anterior or orbital approach, and such a tumor, I believe, should always be approached transcranially. This is a simple classic type, with the tumor in the position in which it is usually found. However, many variations occur that are not nearly so simple.

The second slide shows the area and amount of hyperostosis before and after the operation.

The third slide shows a cavernous hemangioma that became thrombosed; although the pathologic changes were almost entirely limited to the orbit, it would have been impossible to remove this tumor and to save the eyeball by any except a transcranial approach. For these two particular types of tumor, that is, those involving the bony wall and the thrombosed vascular tumors of the orbit, the transcranial method should always be used. For others, however, I think there is still reason for believing that the ophthalmologist can reach most of them from the front.

DR. WALTER E. DANDY, Baltimore: Dr. Benedict's statistics of 25 per cent of growths with intracranial extension, of course, are at variance with my own. I suppose much depends on the field in which one is working. A great many patients with exophthalmos would not consult ophthalmologists, and therefore make the neurosurgeons' statistical results much higher.

I know that the present approach by ophthalmologists is very good for tumors located in certain parts of the orbit, particularly anteriorly, and if one feels sure there is no intracranial extension, there is no

reason, of course, to do the intracranial operation. The trouble is that one never knows, and most of these tumors, even the large ones, do not cause intracranial symptoms.

I think the intracranial approach is the safest way of giving the patient every advantage, particularly as after an incomplete intraorbital approach there would be almost no chance of subsequently curing the patient by the intracranial operation. The only death I have had was due to a huge osteoma that involved a whole temporal region and extended into the hypophysis and surrounded the internal carotid artery. It is a short operative procedure, requiring about an hour, and in safe hands offers far more to the patient than any other operative procedure.

TREATMENT OF INCLUSION CONJUNCTIVITIS WITH SULFANILAMIDE

PHILLIPS THYGESON, M.D.
NEW YORK

The virus disease known as inclusion conjunctivitis or inclusion blennorrhea is an etiologic entity which appears in the newborn infant typically as severe papillary conjunctivitis and in the adult as follicular conjunctivitis with acute or subacute onset. The disease, whether in the adult or in the newborn infant, heals spontaneously after running a course of at least several months. In my series of 52 cases the conjunctiva has never returned to normal in less than three months and has required from four to five months in the majority of cases. In a few cases the condition has persisted more than one year, and in 1 adult it lasted more than two years. The use of the usual conjunctival antiseptics, such as silver nitrate, mercurochrome, phenylmercuric nitrate, mercury oxycyanide, zinc sulfate and quinine bisulfate, which have been employed with success in the treatment of bacterial conjunctivitis, failed to shorten the course. This was illustrated especially well in cases in which the condition was bilateral and only one eye was treated, the other serving as a control.

After the report by Loe [1] that sulfanilamide had proved effective in the treatment of the related virus disease, trachoma, the drug was tested in cases of inclusion conjunctivitis, and a preliminary report [2] described success in the treatment of the experimental disease of Macacus rhesus monkeys and of 2 human beings. Since then in additional cases of infants and adults as well as in cases of the experimental disease in baboons sulfanilamide therapy has been given, and the results are reported herewith.

Aided by a grant from the Francis I. and Elizabeth C. Proctor Fund.

Read at the Seventy-Sixth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 3, 1940.

From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology, Presbyterian Hospital.

1. Loe, F.: Sulfanilamide Treatment of Trachoma: Preliminary Report, J. A. M. A. **111**:1371 (Oct. 8) 1938.

2. Thygeson, P.: Sulfanilamide Therapy of Inclusion Conjunctivitis, Am. J. Ophth. **22**:179 (Feb.) 1939.

SULFANILAMIDE THERAPY OF EXPERIMENTAL INCLUSION CONJUNCTIVITIS IN MONKEYS AND BABOONS

As previously reported,[2] 2 M. rhesus monkeys recovered from experimental inclusion conjunctivitis within two weeks during which sulfanilamide was given in doses of ½ grain (0.03 Gm.) per pound of body weight per day. Two untreated controls still had active disease at the end of the test period.

Four baboons with experimental inclusion conjunctivitis have since been similarly treated with the same dosage. Treatment was begun within one week after onset of the disease and in 2 of the animals was effective in returning the conjunctiva to normal within two weeks. In the other 2 animals all inflammation disappeared but follicles still persisted at the end of the period of treatment. The continuation of treatment for an additional week resulted in disappearance of follicles in one of these animals and in reduction in the number of follicles in the other, in which two small islands of follicular hypertrophy persisted for another month. An untreated control animal continued to show inflammation and follicular hypertrophy without significant change over the three week test period and required slightly more than three months to heal.

These results in monkeys and baboons would appear to be significant, although it must be emphasized that the experimental disease is milder and has a shorter and more variable course than the human disease.

TREATMENT OF INCLUSION CONJUNCTIVITIS IN ADULT HUMAN BEINGS

Table 1 summarizes the results obtained in the treatment of 4 adults with inclusion conjunctivitis. The patients differed somewhat in clinical appearance, 2 having predominant follicular hypertrophy and the other 2 having a more severe condition and showing predominant papillary hypertrophy. In 1 with the follicular condition there were sufficient changes in the corneal epithelium to reduce vision. All the patients responded satisfactorily to sulfanilamide therapy, discharge and inflammatory signs disappearing rapidly and follicular hypertrophy more gradually. A single untreated patient used as a control still had the active condition when last seen two months after onset of symptoms.

TREATMENT OF THE DISEASE IN INFANTS

Table 2 summarizes the results obtained in the treatment of 10 infants with the infection. It will be seen that in the 6 who received adequate treatment (0.1 Gm. per kilogram of body weight for six days or longer) the disease responded even more strikingly and rapidly than

TABLE 1.—*Sulfanilamide Treatment of Inclusion Conjunctivitis in Adult Patients*

Case	Age and Sex	Duration of Symptoms Prior to Treatment	Type of Conjunctival Change	Sulfanilamide Dosage and Level in the Blood per Hundred Cubic Centimeters	Bacteriology	Inclusions	Results
1	34 F	2 weeks	Unilateral; papillary hypertrophy predominant	2 Gm. daily for 13 days; 3 mg. concentration	Normal flora	Numerous first 2 days of therapy; not found thereafter	Rapid cessation of inflammation and discharge; eye normal after 13 days except for few follicles in lower fornix, which soon disappeared
2	30 M	5 weeks	Unilateral; follicular hypertrophy predominant; punctate keratitis reducing vision to 20/30	4 Gm. first day; 3.3 Gm. 2d day; 2.6 Gm. daily for 14 days; 8.6 mg. concentration. Course repeated: 6 to 8 mg. concentration	Few colonies Staph. aureus in 1st culture; normal flora thereafter	Moderate numbers before treatment; absent on two examinations thereafter	All symptoms gone after 1st course; a few follicles still present after 2d course; complete healing
3	31 M	3 weeks	Unilateral; follicular hypertrophy predominant	Azosulfamide 3 Gm. daily for 3 weeks	Normal flora	Small numbers at onset; present 1st and 2d days of therapy; not found thereafter	Rapid disappearance of discharge and inflammation; gradual disappearance of follicles over treatment period
4	26 F	5 days	Bilateral; papillary hypertrophy predominant	Dosage varied to give blood levels from 6 to 9 mg. for 1 week; then 2 Gm. daily for 10 days	Normal flora	Moderate numbers present 1st and 2d days of therapy; not found thereafter	Rapid cessation of inflammation and discharge; conjunctiva normal at end of treatment period
5 Control	40 M	.....	Unilateral; follicular hypertrophy predominant	Untreated	Normal flora	Moderate numbers	Gradual reduction in inflammatory reaction during 6 weeks; severe follicular hypertrophy still present

TABLE 2.—*Sulfanilamide Treatment of Inclusion Conjunctivitis in Infants*

Case	Age and Sex	Duration of Symptoms Prior to Treatment	Type	Dose of Sulfanilamide per Kilogram of Body Weight per Day	Bacteriology	Inclusions	Results
1	5 weeks M	30 days	Unilateral	0.2 Gm. 1st 24 hours; then 0.1 Gm. next 18 days	Normal flora	Numerous first 2 days of therapy; a few present 3d day; none found thereafter	Rapid disappearance of inflammation and discharge; conjunctiva normal at end of period of therapy; no recurrence
2	11 days M	1 day	Unilateral	0.2 Gm. 1st 24 hours; then 0.1 Gm. for 7 days	Normal flora	Numerous first 2 days of therapy; absent thereafter	Rapid disappearance of inflammation and discharge; conjunctiva normal within 10 days; no recurrence
3	3 weeks F	15 days	Bilateral	0.2 Gm. for 24 hours; then 0.1 Gm. for 8 days	Normal flora	Numerous first 2 days of therapy; only 1 inclusion found on 3d day; none thereafter	Rapid healing; conjunctiva normal at end of 9 days of treatment
4	10 days F	3 days	Bilateral	0.1 Gm. for 24 hours; then 0.5 Gm. for 6 days; local sulfanilamide irrigations	Normal flora	Numerous first 2 days of therapy; none found thereafter	Rapid cessation of discharge and disappearance of inflammation; conjunctiva normal within 10 days
5	2 mo., 11 days F	2 mo., 5 days	Bilateral	0.2 Gm. for 24 hours; then 0.1 Gm. for 6 days	Normal flora	Moderate numbers first 2 days of therapy; none found thereafter	Rapid healing; conjunctiva normal within 10 days
6	12 days F	5 days	Unilateral	0.05 Gm. for 6 days	Normal flora	Numerous first 2 days of therapy; a few on 3d day; none found thereafter	Rapid cessation of discharge; all symptoms gone end of 1st week; recurrence 4 days after therapy stopped
7	11 days F	3 days	Unilateral	0.05 Gm. for 4½ days; administration stopped because hemoglobin dropped from 115% to 78%	Normal flora	Numerous first 2 days of therapy; a few 3d day; not found again until recurrence, when again numerous and present 2 months	Rapid cessation of discharge and disappearance of inflammatory signs; recurrence of symptoms with spread to normal eye; still highly active after 2 months
8	17 days F	12 days	Unilateral	0.1 Gm. for 7 days	Staph. aureus found during treatment period; not found 10 days later	Numerous 1st and 2d days; not found thereafter	Rapid disappearance of inflammation and discharge; complete healing
9	13 days M	4 days	Bilateral	0.1 Gm. for 4 days	Esch. coli; not found on later cultures	Numerous 1st 2 days; not found on 3d and 4th days; present again after recurrence	Rapid disappearance of discharge; recurrence 4 days after treatment stopped
10	12 days F	5 days	Unilateral	0.05 Gm. for 6 days	Normal flora	Numerous at start of treatment; present 1st and 2d days; not found thereafter	Rapid disappearance of discharge and inflammation; return of conjunctiva to normal
1 Control	2 mo., M	1 mo., 24 days	Bilateral	Untreated	Normal flora	Present 3 months	Gradual improvement; still active after 3 months
2 Control	8 days F	1 day	Bilateral	Untreated	Normal flora	Present 3 weeks	Could not be followed

it did in the adults and healed within two weeks, without subsequent recurrence. The remaining 4 infants also showed striking response to the drug, but in 3 of them the condition recurred a few days after cessation of treatment and then ran the usual course to healing in periods varying from four to six months. In 2 of these the disease was unilateral to begin with but spread after recurrence to the previously normal eyes.

It would seem from these results that a dose of 0.1 Gm. per kilogram of body weight per day for seven days should effect healing without recurrence in the great majority of cases. It must be noted that in 1 case (10) a dose of 0.5 Gm. per kilogram for six days effected permanent healing but that there was a recurrence in case 6, in which the same dose was administered over the same period, and that in case 7 the same dosage for four and one-half days was also insufficient.

EFFECT OF LOCAL SULFANILAMIDE THERAPY

Table 3 summarizes the results obtained in 2 infants with inclusion blennorrhea treated locally with a saturated 0.8 per cent solution of sulfanilamide in physiologic solution of sodium chloride. In the first case no effect was obtained from the use of the solution as a collyrium four times daily, but in the second case its use every fifteen minutes during the day and every hour during the night for seven days was temporarily beneficial. Further experimentation with other preparations, such as ointments or emulsions to obtain more prolonged action of the drug, would seem to be in order.

EFFECT OF SULFANILAMIDE ON THE INCLUSION BODIES

As indicated in tables 1 and 2, sulfanilamide therapy produced a striking effect on the microscopic picture of the disease, as seen in Giemsa-stained epithelial scrapings. In all cases the inclusion bodies could be demonstrated without difficulty during the first and second days of treatment but were either reduced sharply in numbers or absent on the third day and could in no case be found after the third day. In the 3 cases in which the disease recurred inclusions were demonstrable at the time of the return of symptoms.

The morphologic and staining reactions of the inclusions and free elementary and initial bodies seen during the first two days of therapy appeared to be normal, but on the third day the poor staining of an occasional one of the few remaining inclusions and the lack of sharpness of its component elementary and initial bodies suggested a process of degeneration.

Sulfanilamide therapy also had a striking effect on the leukocyte picture. Before treatment epithelial scrapings were always loaded with

TABLE 3.—*Local Treatment with Sulfanilamide*

Case	Age and Sex	Duration of Symptoms Prior to Treatment	Type	Sulfanilamide Dose	Bacteriology	Inclusions	Results
1	6 days M	1 day	Unilateral	0.8% solution 3 times a day for 1 month	Normal flora	Numerous	No effect; disease still active at end of 4 months
2	9 days F	2 days	Unilateral	0.8% solution instilled into eye every 15 minutes during day and every hour during night for 7 days	Normal flora	Numerous at start of treatment; not found 4th to 7th day; numerous after recurrence	Rapid cessation of inflammation and discharge; recurrence few days after treatment was stopped, with spread to normal eye; condition still active at end of 4 months

polymorphonuclear leukocytes, but during treatment the number of leukocytes in relation to the number of epithelial cells rapidly diminished until, by the fifth or sixth day, scrapings contained almost no cells except epithelial cells.

EFFECT OF SULFANILAMIDE ON THE INFECTIVITY OF THE DISEASE IN BABOONS

As has been noted by Lindner and others, the baboon is probably the animal of choice for experimental work with inclusion blennorrhea, since all species tested have been susceptible and have reacted uniformly to test inoculations. In my experience infection has always occurred when adequate material from inclusion-bearing patients has been employed. It has also been my experience that the inoculation of baboons is a more sensitive test for the presence of the virus of inclusion blennorrhea than the microscopic test, since infection has been obtained in baboons with material from old cases in which inclusions could be demonstrated only after repeated examinations.

In an effort to obtain data on the effect of sulfanilamide on the virus, baboons were inoculated at intervals with material from 4 patients under treatment. The results are recorded in table 4. While the experiments are too few to permit conclusions to be drawn, it is of interest that material taken on the second day of treatment, when numerous inclusions could still be demonstrated, failed to infect baboons in 2 of 3 instances. On the other hand, material from 2 patients produced infection in baboons on the fifth and sixth days of therapy respectively at a time when inclusions could no longer be demonstrated in epithelial scrapings. The latter finding would confirm the opinion that the baboon inoculation test is more sensitive than the microscopic test.

EFFECT OF SULFANILAMIDE ON THE BACTERIAL FLORA

Unlike trachoma, inclusion conjunctivitis is only rarely complicated by secondary bacterial infection. As indicated in tables 1, 2 and 3, the flora was normal in all but 3 cases of this series. Treatment with sulfanilamide had no effect on Corynebacterium xerosis or Staphylococcus albus. In 1 case (9, table 2), in which there were moderate numbers of colonies of Escherichia coli at the onset of treatment, subsequent examinations failed to show the organism. In a second case (2, table 1) there were a few colonies of Staphylococcus aureus during the first week of treatment, but three subsequent examinations showed only normal flora. In a third case (8, table 2) there were moderate numbers of colonies of Staph. aureus before, during and immediately after treatment, but three subsequent cultures failed to show the organism.

TOXIC REACTIONS DUE TO SULFANILAMIDE

Except for the drop in hemoglobin and red cell count which occurred in 1 infant (case 7, table 2) there were no significant toxic reactions to sulfanilamide in the cases of this series. Two of the adults complained

TABLE 4.—*Effect of Sulfanilamide on the Infectivity of Inclusion Blennorrhea*

Case	3*	7	6	5
Sulfanilamide dosage per Kg. per day	0.2 Gm. 1st day; then 0.1 Gm. for 8 days	0.05 Gm. for 4½ days	0.05 Gm. for 6 days	0.2 Gm. 1st day; then 0.1 Gm. for 6 days
Before treatment....	Inclusions numerous; baboon inoculation positive	Inclusions numerous	Inclusions numerous; baboon inoculation positive	Inclusions numerous; baboon inoculation positive
1st day.....	Inclusions numerous; baboon inoculation positive	Inclusions numerous; baboon inoculation positive	Inclusions numerous	Inclusions numerous
2d day.....	Inclusions numerous; baboon inoculation negative	Numerous inclusions	Inclusions numerous; baboon inoculation positive	Inclusions numerous; baboon inoculation positive
3d day.....	Only 1 inclusion found; baboon inoculation negative	A few inclusions; baboon inoculation positive	No inclusions; baboon inoculation negative	No inclusions
4th day.....	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation negative	.....	.....
5th day.....	.....	No inclusions	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation positive
6th day.....	No inclusions; baboon inoculation positive	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation negative
7th day.....	No inclusions	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation negative	No inclusions; baboon inoculation negative
8th day.....	No inclusions	.....	.....	.....
End result.....	Healing; no recurrence	Disappearance of symptoms, followed by recurrence	Disappearance of symptoms, followed by recurrence	Healing; no recurrence

* Case numbers refer to those on table 2.

of some headache and a feeling of depression while under treatment. The infants tolerated the drug well and in each instance gained normally in weight while under treatment.[3]

3. The sulfanilamide was administered to the 10 infants under the supervision of the department of pediatrics. Dr. Rustin McIntosh and his staff cooperated in this study.

COMMENT

As indicated by the rapid healing obtained in this series, it may be stated that sulfanilamide has a definite curative action on inclusion conjunctivitis. Since secondary bacterial infection is rare and when present appears to play little if any part in the evolution of the disease, it must be concluded that the drug acts directly on the virus itself. This conclusion is supported by the results of the baboon inoculation experiments and by the fact that the inclusions, which are known to represent microcolonies of virus, disappear sharply between the third and fourth days of therapy.

The adults in whom follicular hypertrophy predominated responded more slowly to the drug than those with predominant papillary hypertrophy or than the infants. This same difference in the rate of healing has been noted [4] in trachoma, in which stage IIb (papillary) trachoma heals rapidly whereas the follicles of stage IIa (follicular) trachoma often persist for many weeks after all inflammatory signs have disappeared. The rapid response of inclusion blennorrhea in the infant is probably due to the fact that lymphoid follicles do not develop in the conjunctiva of the newborn infant. The nonspecific cellular infiltration disappears rapidly on disappearance of the virus.

There is no information available as to the exact mechanism of action of the drug on the virus. It seems probable, however, on the basis of microscopic observations, that the sulfanilamide acts to stop intracellular development of the virus. The rather sudden disappearance of the virus, as represented by the inclusion bodies, on the third and fourth days is probably the result of the normal desquamation of superficial epithelial cells. It is known from the histologic studies of Braley [5] and others that the inclusions occur in the upper and middle layers of cells rather than in the basal layers.

It is significant that only three viruses, those of trachoma, lymphogranuloma venereum and inclusion blennorrhea, have responded with certainty to sulfanilamide and its derivatives. These three and the virus of psittacosis form a group of atypical viruses which differ from the typical viruses of large particle size in three main characteristics: (*1*) they form basophilic heterogeneous inclusions rather than acidophilic homogeneous inclusions; (*2*) they show a sequence of morphologic variation from small filtrable forms to large forms the size of small bacteria, a variation which typical viruses do not show, and (*3*) their

4. Thygeson, P.: The Treatment of Trachoma with Sulfanilamide, Tr. Am. Ophth. Soc. **37**:395, 1939; Am. J. Ophth. **23**:679 (June) 1940.

5. Braley, A. E.: Inclusion Blennorrhea: A Study of the Pathologic Changes in the Conjunctiva and Cervix, Am. J. Ophth. **21**:1203 (Nov.) 1938.

elementary bodies stain rapidly and well with Giemsa and similar stains, whereas the elementary bodies of typical viruses require mordants or prolonged staining for demonstration. It would be logical to expect that the virus of psittacosis might also be susceptible to chemotherapy, but there have been no reports to that effect.

SUMMARY

Sulfanilamide proved effective in causing rapid healing of inclusion conjunctivitis in infants and adults as well as of the experimental disease in monkeys and baboons.

Adults with predominant papillary hypertrophy responded more rapidly than those with predominant follicular hypertrophy.

The characteristic epithelial cell inclusions could always be demonstrated during the first two days of therapy but could not be found after the third day. Infectivity of epithelial scrapings for baboons also disappeared during treatment.

DISCUSSION

Dr. Frederick C. Cordes, San Francisco: I had an interesting experience that coincides with Dr. Thygeson's. Approximately two months ago a patient, who had been treated for several months by various oculists, came into the office with an inflammation of the lid corresponding closely to the one described by Dr. Thygeson. After various therapeutic measures had been tried, all therapy was discontinued with the thought that possibly lack of improvement in the condition might be a matter of overtreatment. In spite of this, the condition did not improve, and in sheer desperation it was decided to try sulfanilamide. Within a week the acute symptoms had subsided, and by the end of three to four weeks the conjunctivitis was practically gone. Unfortunately, in this case no laboratory examinations were made, but I feel that I was probably dealing with a condition similar to that described by Dr. Thygeson.

Dr. James H. Allen, Iowa City: I wish to confirm some of Dr. Thygeson's observations. I have had the opportunity of treating 18 patients with sulfanilamide at the University of Iowa Hospital. This drug has been used locally in some diseases and has been found to be of benefit. Therefore I tried 0.5 per cent sulfanilamide ointment locally in 3 patients. In the first the inclusion bodies disappeared on the fourth day of treatment, and the treatment was continued for a total of ten days. At the end of that time there was considerable clinical improvement and the patient was discharged. He was observed at the end of one month, and at that time the conjunctivas appeared normal. On the basis of this apparent success I tried the treatment in 2 other cases. The ointment was applied every four hours for ten days, but in these 2 cases the inclusion bodies persisted. At the end of that time the oral administration of sulfanilamide was tried; the inclusion bodies disappeared on the fourth day, and clinical improvement was observed

in ten days. One month after institution of therapy the conjunctivas appeared normal. In the remaining 15 cases the drug was administered orally.

In the adults my dosage was similar to that of Dr. Thygeson, that is, ⅓ to ½ grain of sulfanilamide (0.02 to 0.03 Gm.) per pound of body weight per day for ten days. With this dosage I found that the level of the free sulfanilamide in the blood ranged around 3 mg. per hundred cubic centimeters. In infants the dosage was somewhat higher because of the method of administration, and it was calculated at 1½ grains (0.1 Gm.) per pound of body weight per day. The drug was suspended in the milk formula and given to the infant with its feedings. The infant did not always get the calculated dose and because of regurgitation probably lost some of the drug, but the level in the blood ranged around 3 mg. per hundred cubic centimeters. With this concentration in the blood 2 of the children showed inclusion bodies for five days after administration of the drug. A few showed inclusion bodies for only three days after the institution of therapy, but the majority did not show inclusion bodies after the fourth day of treatment. The clinical course was similar to that in Dr. Thygeson's cases. There was no secondary bacterial infection.

Dr. Phillips Thygeson, New York: I have just started experimentation in the local use of sulfanilamide and have only 2 cases which can be reported. In the first case the use of a saturated solution of sulfanilamide, that is 0.8 per cent, four times daily in the form of irrigations failed to affect the clinical course in any way or to influence the persistence of the inclusion bodies. In the second case local instillations of the same saturated solution were given every fifteen minutes during the day and every half hour at night for one week. There was satisfactory improvement, and at the end of the week there was no longer any conjunctival discharge and only slight persistent inflammatory reaction. Three days after the therapy was stopped the disease recurred with full intensity and is now running the same clinical course as in the untreated patients.

NEUROMYOARTERIAL GLOMUS TUMOR IN THE EYELID

DANIEL B. KIRBY, M.D.
NEW YORK

The normal glomus has been known to exist in the hands and feet. It is a peculiar anastomosis of arteries and veins, thickened by the presence of smooth muscle fibers, nerve fibers and peculiar "epithelioid glomus cells." [1] It probably shares in the control of the circulation of the blood, particularly in the extremities, and in the regulation of the local and general temperature of the body. The occurrence of benign glomus tumors,[2] arteriovenous networks surrounded by nerve, muscle and glomus cells elsewhere in the body, suggests that the normal glomus may be present in other areas, but so far no one has been able to demonstrate it. I have studied sections of the skin of the eyelids, and no glomus has been revealed. If any are present, they must be exceedingly uncommon, and none has been reported. I have encountered a neuromyoarterial glomus tumor in the left lower eyelid of a South American native, a 30 year old man of Inca Indian and Spanish extraction. His family and personal history were irrelevant except that his brother had glaucoma. The tumor, which measured 5 by 8 by 18 mm. (fig. 1), was located beneath the skin and attached to it. The growth had appeared first eight years previously, had been surgically removed four years previously and had recurred two years previously. The clinical diagnosis of melanoma, made by me before removal of the growth, may be explained by the large amount of melanin in the epidermis and in the cells beneath it. The typical history of paroxysmal attacks of pain and disturbances of the sympathetic nervous system usually associated with the development of this benign tumor in the extremities, for example, in the digits, was not elicited in this case. The tumor was not responsive to changes in outside temperature but was sensitive to light touch and to deep pressure. Since the removal

Read at the Seventy-Sixth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 3, 1940.

1. Masson, P.: Les glomus cutanés de l'homme, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **42**:1174-1245, 1935; IV Les glomus neurovasculaires histophysiologie, Paris, Hermann & Cie, p. 453.

2. Eight to twelve references appear each year in the Quarterly Cumulative Index Medicus under Tumors, Neuromyoangioma and Glomangioma.

of the growth by me (April 11, 1939) by wide surgical excision, with a plastic sliding graft of subcutaneous tissue to fill the deep gap and the use of a free skin graft from the upper eyelid to remedy the superficial fault, there has been no sign of recurrence. A minor tendency to keloid formation beneath the graft was controlled by two roentgen treatments, given by Dr. Maurice Lenz. The scar became soft and

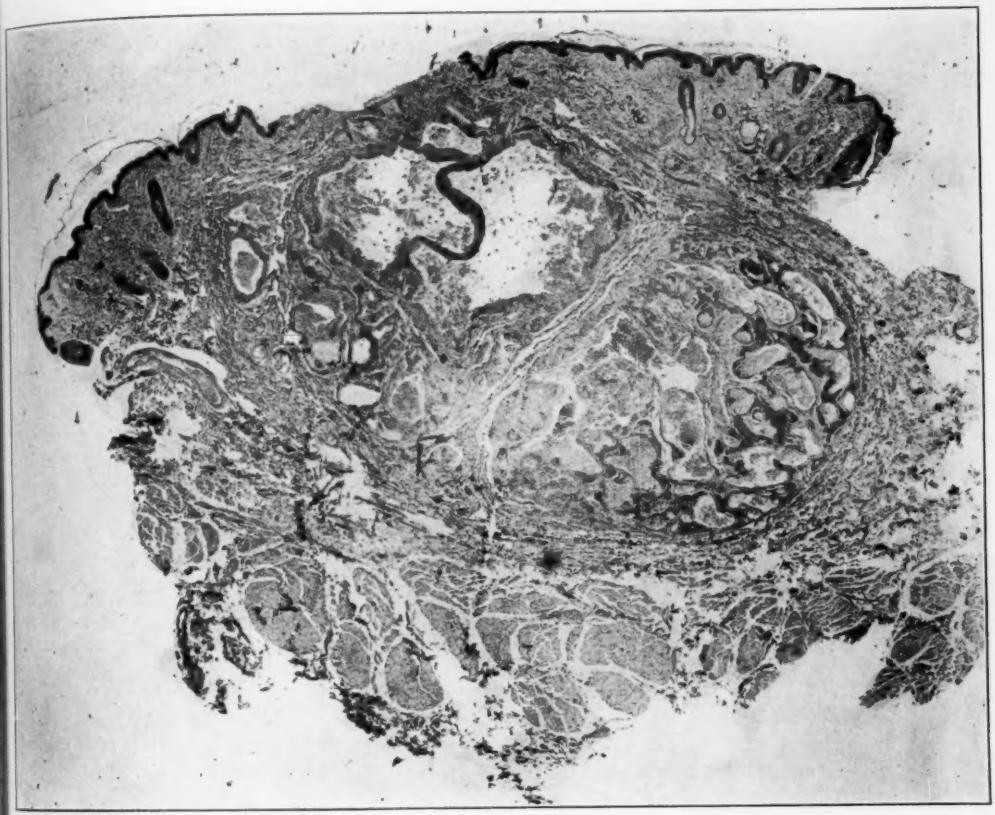


Fig. 1.—Low power photomicrograph of the entire neuromyoarterial glomus tumor of the eyelid. The capsule surrounding the mass is intact.

smooth, without pigmentary changes. The microscopic appearance was that of a tangled mass of blood vessels within a capsule. The vessels were lined with a single layer of endothelium supported by a fibrous layer varying in thickness. The vessels varied a great deal in caliber, some having dilated lumens similar to those of cavernous hemangiomas. The majority of the vessels had no recognizable smooth muscle fibers. The rest of the walls of the blood vessels was made up of the peculiar

cuboid or rounded "glomus" cells usually referred to as "epithelioid" cells because Masson so described them (fig. 2). These cells had well defined outlines framed by delicate collagen fibers. The cytoplasm was pale and sometimes vacuolated, and the nucleus was large, central and globular or ovoid. Stout's monograph [3] on the subject is worthy of careful study.

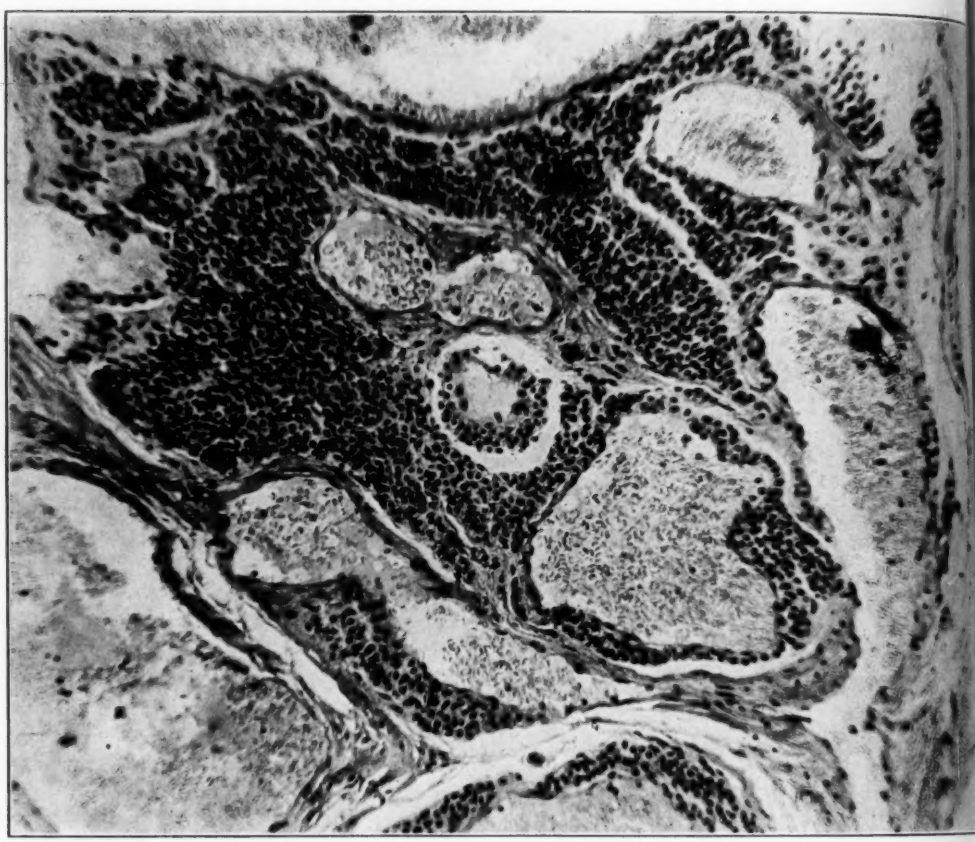


Fig. 2.—Medium power photomicrograph of the tumor, showing vascular spaces, the walls of which are thickened with epithelioid cells.

REPORT OF A CASE

The patient was a native of Peru, an office worker, aged 30.

History.—The family history was unimportant except that one brother had had glaucoma. The patient said that his mother had told him that he had been an unhealthy baby, with some sort of stomach trouble, but that he had made a

3. Stout, A. P.: Tumors of the Neuromyo-Arterial Glomus, Am. J. Cancer **24**:255-272, 1935.

complete recovery at the age of 4 years. He remembered no other childhood illnesses. He had had appendicitis and had undergone appendectomy at 15 years of age. He had suffered from malaria at 20; he had been treated with quinine and plasmochin and had had no recurrence. He had had no venereal disease. Mumps had occurred in January 1939, followed by orchitis; he had spent sixteen days in bed. At the age of 15 he had had what he called a nervous breakdown, which he said was due to overwork. He had thought that he had heart trouble but had been convinced later that there was no cardiac involvement. Several times since then, whenever he had been overtired, he had had the same symptoms of worry and depression, but these had always been relieved by a brief period of rest.

Physical Examination (Dr. John E. Sawhill).—The patient was 5 feet 6 inches (167.6 cm.) tall and weighed 157 pounds (71.2 Kg.). The teeth showed some areas of absorption around the roots. The tonsils were enlarged but apparently not diseased. Both auricular canals showed a moderate degree of eczema. There was no enlargement of the lymph glands. There was a normal thyroid, not palpable. The basal metabolic rate was +9 per cent. The heart was normal in size and shape. There were no abnormal signs. The blood pressure was 114 systolic and 74 diastolic. The chest was clear. The abdomen showed the appendectomy scar; there was no tenderness; no masses were palpated. The extremities were normal. All the reflexes were apparently normal. The vibratory sense was normal. Rectal examination gave negative results.

Laboratory Data.—The Wassermann reaction was negative. The urine was normal. The value for dextrose was 85 mg. and that for nonprotein nitrogen 34.6 mg. per hundred cubic centimeters of blood. The blood count and the value for hemoglobin were normal.

Examination of Eyes.—The lids and the tumor were as described. The conjunctivas were normal. The corneas, pupils, uveas, media and fundi were normal. Vision was 20/20 in each eye without correction, practically emmetropic. The fields and the blindspots were normal. The intraocular tension in each eye was 17 mm. of mercury (Schiötz). The extraocular muscles showed normal excursions, coordination and third degree fusion. Tests of the urine for melanin gave negative results, as did the white rat test for malignant tumor.

The pathologic diagnosis was furnished by Dr. Arthur Purdy Stout, who reported: "This is a characteristic tumor of the neuromyoarterial glomus." The tumor lay in the deeper layers of the corium and in the subcutaneous tissue. It was composed of a congeries of blood vessels (fig. 2), many of which were dilated and filled with red blood cells. In the walls of these vessels were masses of closely placed, rounded cells (fig. 3) with centrally located nuclei and a rather clear zone in the cytoplasm about the nucleus. Each cell had a clearly defined cell membrane and was separated from its neighbors by delicate strands of collagen (fig. 4). There was little smooth muscle associated with any of the vessels. Some nerve bundles were recognized at the periphery of the tumor (fig. 5).

Stout stated that so far as he is aware the existence of the normal glomus elsewhere than in the hands and feet has not been proved. The occurrence of glomus tumors elsewhere in the body suggests that they may be present in other areas, but so far no one has been able to demonstrate them. In answer to a personal query, Dr. Stout said: "I do not think that it would pay to study casual sections of the skin around the eyelids in the hunt for glomuses, because if they are present

they must be exceedingly uncommon. Only painstaking search through a great many serial sections would have any chance of success." It would also be necessary to reconstruct a three-dimensional schema to appreciate the glomus.

The normal glomus, or glomic unit, is found in the deeper layers of the corium, particularly abundant in the skin and in the nail matrix

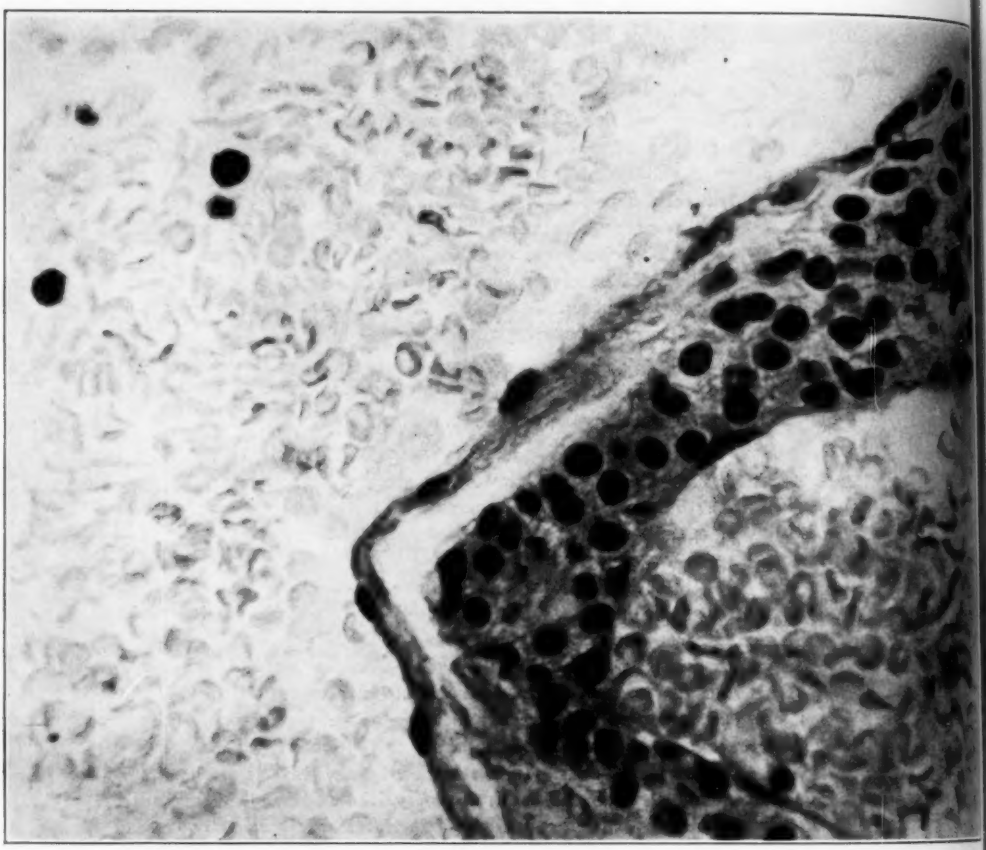


Fig. 3.—High power photomicrograph of the wall of tissue separating two large vascular spaces in the tumor.

of the digits, where Popoff counted eighteen to twenty-four in cross section; a much better concept can be obtained by serial sections. From studies of this kind Popoff [4] was able to build up his original schema

4. Popoff, N. W.: Recherches sur l'histologie des anastomoses artério-veineuses des extrémités et sur leur rôle en pathogénie vasculaire, Bull. d'histol. appliq. à la physiol. **12**:156-171, 1935; footnote 8.

or diagram (fig. 6). The arterial portion of the glomus is derived from the subcutaneous vessels which run parallel to the cutaneous surface. Small arteries come off at right angles to the parent vessel, and each promptly divides into two branches. The lesser of these breaks up into capillaries to supply the various structures in the skin. The larger branch leads off at almost right angles into from one to four

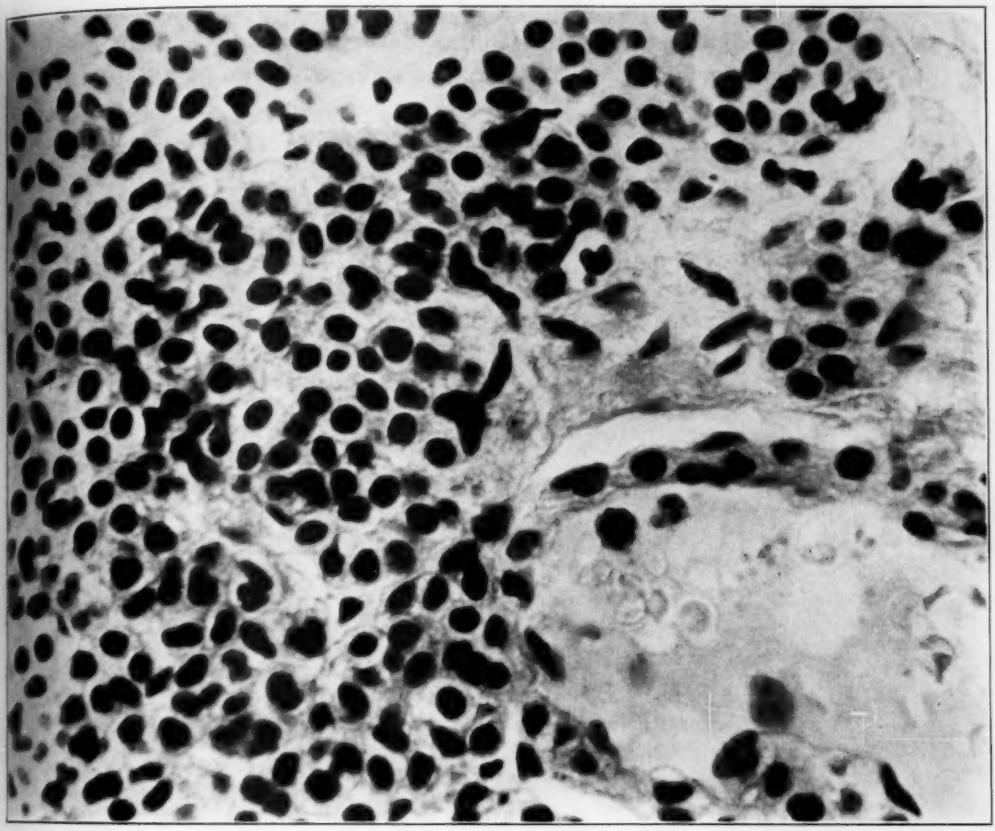


Fig. 4.—High power photomicrograph of the glomus cells. The vascular spaces are lined by endothelium. Cuboid glomus cells, smooth muscle fibers and nerve filaments thicken the walls of the vascular spaces.

Sucquet-Hoyer canals.[5] As the vessel approaches the canal, the muscular layers narrow and the internal elastic lamina ends. Here the endothelium is thrown up into folds or ruffles by a cushion-like projection of collagenous tissue and the termination of the elastic lamina.

5. Sucquet and Hoyer, cited by Popoff.[4]

The function of these folds seems to be to direct the flow of blood into the canals and the preglomic arterioles, which arise at this point to supply all the glomic structures.

The venous portion of the glomus is represented by a plexus of thin-walled veins having a vast surface area and very few muscular elements in their walls. The venous plexus is in direct communication with the deep veins. Of particular interest is the Sucquet-Hoyer canal itself. It is a twisting, S-shaped tubule with an irregular lumen, which is narrow but has great possibilities for expansion. The endothelial cells are voluminous and cuboid and are arranged in two or three rows.

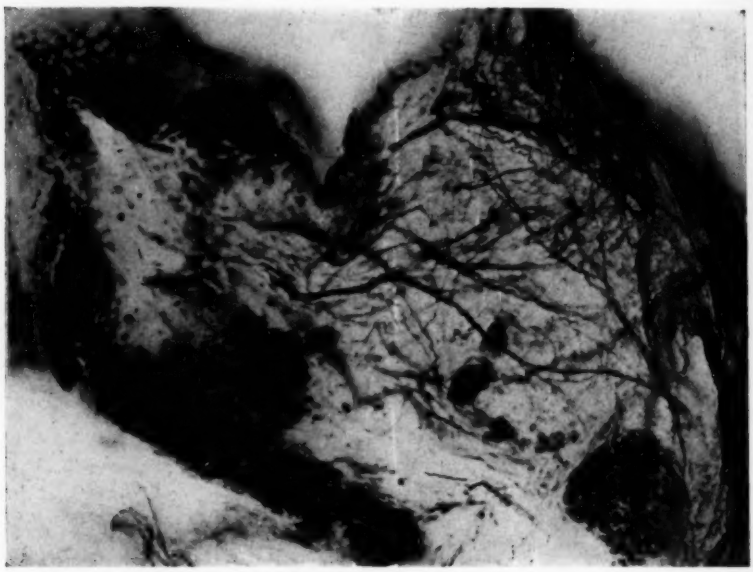


Fig. 5.—Abundant nerve filaments in a case of neuromyoarterial glomus tumor of the extremity (Stout [3]).

Outside the endothelial layers are muscular elements, but it is impossible to differentiate distinct layers of circular and longitudinal muscle as in the usual arteriole, and the elastic laminas are absent. Between the muscle cells are found epithelioid cells [6] with oval or globular nuclei, poor in chromatin and having a vacuolated cytoplasm. The exact nature of these cells in unknown,[7] but they are probably related to smooth muscle, as smooth muscle fibers are occasionally found in them.

6. Masson, P.: Le glomus neuro-myo-artériel des régions tactiles et ses tumeurs, Lyon chir. **21**:257, 1924; cited by Stout.[3]

7. Culture of tissue or of the living cell may in the future supply knowledge which the study of fixed preparations has been unable to give.

They are probably not nerve cells, as they give no staining reaction of nerve cells and nerve fibers are never found in them in spite of the fact that the area is freely supplied with nerve fibers. Beyond the muscle cells is a loose, delicate collagenous reticulum, in which are numerous nonmedullated nerve fibers. The entire glomus is surrounded by a coarse lamellated collagenous tissue, in the meshes of which are seen the collecting veins.

The physiologic character of these glomic units is not well understood, but it is apparent that they represent an important physiologic short circuit between the arterial and the venous channels. Their structure suggests that they may act to regulate peripheral arteriolar and

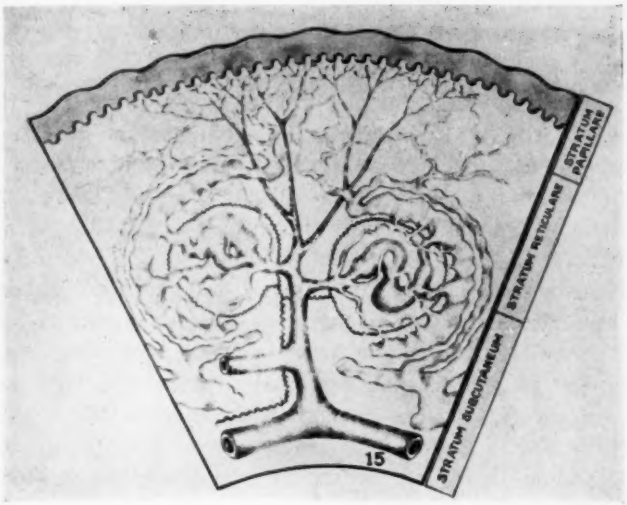


Fig. 6.—Popoff's schematic diagram of the normal glomus (Stout [3]).

capillary pressures and that they must act to play some part in the control of temperature.

The vast surface area of the collecting veins, through which an enormous amount of blood may be poured in short units of time, suggests that when these anastomoses are thrown open radiation of heat is accelerated. The throbbing and superficial pulsation associated with the pain of inflammation of the skin of the digits is probably a direct effect of the opening of the glomuses. Occasionally a patient with infected chalazia will complain of throbbing pain in the eyelid. This may be an indication of opening of glomuses in the eyelids. It is of interest that the fetus has no glomic units and that these units develop

during the first few months after birth. Popoff [8] suggested that the fetus has no need for temperature regulation units and that until they are developed the infant, particularly if premature, is unable to regulate body temperature properly.

It is hardly necessary in this paper to consider the changes that may take place in the glomic units as a result of vascular disease. Popoff expressed the belief that they play an important part in the explanation of the local phenomena of inflammation and of vascular disease. The strictly localized heat in the presence of inflammation, the color changes in thromboangiitis obliterans and the coldness of the digits in senile arteriosclerosis may all be dependent in some fashion on changes in these minute physiologic anastomoses.

DIFFERENTIAL DIAGNOSIS OF GLOMUS TUMOR

While a positive diagnosis can be made only by microsection, the clinical course and symptoms of a glomus tumor of an extremity are so characteristic that as a rule a reasonably certain clinical diagnosis should be made. It should be simple to rule out exostosis, papilloma, nevus, lipoma, fibroma and sebaceous cyst. The difficulty would be to differentiate the glomic tumor from a single small superficial neuroma and from certain forms of melanoblastoma and melanosarcoma. The pain is believed to be caused by the pressure on adjacent paccinian [9] corpuscles associated with the dilatation of the glomic walls. In a typical case there may be, for example, a tumor of a finger, lying in the deeper layers of the corium in skin and nail matrix, with intolerable pain, stopped by interrupting the circulation through the tumor, and with a tendency toward increased local temperature. Such a tumor acts like an arteriovenous fistula, permitting an abnormal flow of blood. Pressure or jarring stirs it up to cause pain. The fact that none of the typical features of the glomus tumor were present in my patient's tumor of the eyelid may be offered as an excuse for the fact that it was not differentiated until it had been sectioned and studied microscopically.

SUMMARY AND CONCLUSIONS

A typical neuromyoarterial glomus tumor has been encountered for the first time by me in the eyelid of a patient. The normal glomus, a peculiar anastomosis of arteries and veins, thickened by the presence

8. Popoff, N. W.: The Digital Vascular System, with Reference to the State of the Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thrombo-Angiitis Obliterans and Supernumerary Digits in Man, Arch. Path. **18**: 295-330 (Sept.) 1934.

9. Ruffini, A.: Les expansion nerveuses de la peau, Rev. gén. d'histol. **1**:427-437, 1905.

of epithelioid cells, has been demonstrated in the skin of the extremities, particularly in the digits, but never elsewhere. It would be difficult to demonstrate glomuses in the skin of the lids, for if they are present there are very few. The occurrence of a glomus tumor in the eyelid, as in any other part of the body, indicates that normal glomuses probably are present, although this has not been proved. The tumor is benign. In the case reported the typical severe recurring painful attacks were not experienced by the patient. The condition is reported because it is of interest histologically and physiologically and because its occurrence is unique.

ABSTRACT OF DISCUSSION

DR. F. H. VERHOEFF: Dr. Kirby sent me a section of this tumor and sent the diagnosis with it. This was fortunate for me, because I am sure I should not otherwise have recognized the tumor. I was familiar with the fact that such tumors exist in the skin, and this tumor was so characteristic that it was impossible to doubt the correctness of the diagnosis. I congratulated Dr. Kirby on his diagnosis, and I do so again. I think that it is a remarkable thing to find a tumor of the lid that has never been seen or recognized before. I have an indistinct recollection that I have seen a glomus tumor of the lid, but I am sure I did not recognize it.

DR. DANIEL B. KIRBY: I shall not take the bow for myself, for it was Dr. Arthur Purdy Stout who really discovered the tumor. I should not have recognized it. I confess that I knew nothing about it before we had the microscopic diagnosis.

MALIGNANT MELANOMA OF THE UVEAL TRACT

AN ANALYSIS OF FORTY-TWO CASES

S. HANFORD McKEE, M.D.
MONTREAL, CANADA

Since 1924, 42 cases of sarcoma of the uveal tract have come under observation. While in many of the cases the length of time elapsed is too short to allow any deduction, the follow-up begun some years ago has been kept up, and in time this will lead to some useful clinical information.

The disease is relatively rare. Stallard stated that from 1925 to 1931 at Moorfields, sarcoma of the choroid was found in 1 of every 4,000 cases. It is one of the most malignant of ocular diseases. Fortunately, it rarely occurs in both eyes. The prognosis as regards life in a large percentage of cases is absolutely unfavorable. Local recurrences in the orbit and general metastasis frequently develop after removal of the eye. Of a series of cases reported by von Hippel in 1933, evidence of metastasis was present in 38 per cent. In the majority it occurred within five years of the enucleation.

Of the 42 patients whose cases are recorded here 23 were men and 19 were women. The age incidence was as follows:

Under 20 years	1
20 to 29	3
30 to 39	5
40 to 49	7
50 to 59	9
60 and over	17

In the great majority of cases it was some visual disturbance that brought the patient to consultation. In 5 there was a definite history of previous injury to the eye, and in this respect the case of patient P. was of considerable interest.

In July 1939 this patient, a man of 61, presented himself with a history of a blow in the eye some days previously. While sitting in a street car he had received a severe accidental blow with the end of an umbrella, since which time his sight had been very defective. Examination showed a large sheer detachment, and naturally, with this history, a search for a

Read at the Section on Ophthalmology of the Canadian Medical Association, Toronto, Canada, June 1940.

retinal hole was undertaken. No retinal hole was found, and subsequent study of the case led to a diagnosis of sarcoma of the choroid. Enucleation revealed a large malignant growth as the cause of the detachment.

Another case of much interest was one referred by my associate Dr. Stuart Ramsey. An eye had been removed from a man of 56, who had been advised to have it removed seventeen years previously. In the interim he had been advised a number of times by a number of physicians to have his eye removed because of a tumor growth. The eye was removed recently because of severe pain and showed a moderate-sized sarcoma of the ciliary body, of the spindle cell type, subtype B.

In 1931 Callender [1] described four or perhaps five specific types into which all primary malignant uveal neoplasms may be classified.

1. *The Spindle Cell Type.*—This consists of sheets, whorls and other irregular arrangement of spindle-shaped cells with long oval nuclei. The ends of the cell appear to terminate in fibers, so that the cells resemble fibroblasts. There is no argentophil reticulum except that accompanying the nutrient vessels. These spindle cell tumors can be separated into two divisions by the nuclear characteristics.

Subtype A: The nucleus has a delicate reticular structure in which the nucleolar material is not well defined. These tumors are usually fairly heavily pigmented.

Subtype B: The cell has a sharply defined, deeply stained, small, round nucleolus, usually situated near the center of the nucleus, in a rather coarse nuclear network, and is usually lightly pigmented.

2. *The Fascicular Type.*—The cells of this type are elongated, sometimes forming fiber-like structures, but rounded and polygonal shapes are seen. The characteristic nucleus is oval, has a distinct nucleolus and closely resembles the nucleus of the spindle cell, subtype B. The majority of the cells are arranged in columns or fasciculi, the long axis of the cell being at right angles to that of the column. The cells radiate about the center of the column in a palisade arrangement, the center being a lymphatic or capillary blood vessel. Pigmentation is usually scanty.

3. *The Epithelioid Type.*—This type shows polygonal cells, usually relatively large, though there is considerable variation in both size and shape. The nucleus is large and round or somewhat oval, and the nucleolus is distinct. This type varies greatly in the degree of pigmentation.

4. *The Mixed Cell Type.*—This type is composed of irregular mixtures of spindle and epithelioid types of cells, with occasional areas of the fascicular type. The tumors are very heavily pigmented.

---

1. Callender, G. R.: Malignant Melanotic Tumors of the Eye, Tr. Am. Acad. Ophth. **36**:131, 1931.

In this series of 42 cases the sarcoma was primary in the choroid in 37, in the ciliary body in 3 and in the iris in 2. The cellular classification has been altered from time to time during prolonged study. At present it stands as follows:

Spindle cell, subtype A	14 cases
Spindle cell, subtype B	6 cases
Fascicular cell	4 cases
Epithelioid cell	12 cases
Mixed cell	5 cases
Not typed	1 case

This result means, according to Callender's report, that in 30 per cent of my cases the prognosis should have been (and is, in fact) excellent. Likewise, in the other 70 per cent the prognosis is bad. Von Hippel suggested that metastasis occurs in about 50 per cent of the cases.

In the follow-up of this series the following facts have been established. Ten patients have died, but only 8 of the deaths were attributable to the malignant disease. The first of the other 2 patients, a man aged 61 at the time his eye was removed, died of cardiorenal disease five years after the enucleation. The second, a man aged 65 when his eye was removed, died of suspected heart disease four years after the enucleation. It must be stated, however, that in his case there was an indefinite history of enlargement of the liver but no postmortem examination was obtained. In 8 cases death was due to multiple metastasis. Postmortem examination was made in 4 of these. The first of the autopsies was performed on A. L., a man aged 50, who was sent to the hospital in February 1924 with a diagnosis of detachment of the left retina and sarcoma of the choroid. The eye was enucleated. He was readmitted to the medical ward in March 1925, that is, a year later, and died the following April. The autopsy report in part was as follows: "Melanotic metastasis in the dura mater, brain, occipital bone, clavicle, third rib, diaphragm, pericardium, peritoneum, mesenteric and mediastinal lymph nodes, epicardium, myocardium, liver, pancreas, left kidney, adrenals, vesical mucosa, great omentum, thyroid gland and eleventh thoracic vertebra. The liver showed extensive metastasis and extended to the level of the anterior superior spine in the midcenter line."

The tumor cells in these 8 cases were reported on as follows:

Spindle cell, subtype B	1 case
Fascicular cell	1 case
Epithelioid cell	3 cases
Mixed cell	2 cases
Not typed	1 case

Of the living patients, some already prove to be of considerable clinical interest. Patient J. L. had her eye enucleated in 1924, at the age

of 33 years, and is alive and well. J. C., aged 59 years, had his eye removed in 1926 and is alive and well. T. D., aged 62 years, had his eye removed in 1926 and is alive and well. S. B., aged 61 years, had her eye removed in 1927 and is alive and well. Miss N., aged 21 years, had her eye removed in 1928; she has since married and is alive and well. A. P., aged 56 years, had his eye removed in 1930 and is alive and well. Mrs. B. T., aged 47 years, had her eye removed in 1930 and is alive and well. Mrs. U., aged 72 years, had her eye removed in 1932 and is alive and well. All of the tumors were of type A of Callender's grouping except 2, 1 of which was fascicular, while the other was epithelioid.

Following Callender's classification by cell type, Callender and Wilder [2] further classified these tumors by their argyrophil fiber content. They expressed the belief that sections of heavily pigmented melanomas should be rather thoroughly bleached in potassium permanganate and hydrobromic acid before impregnation with silver. Their "fiber classification" divides the tumors into three groups:

1. Tumors having no fibers or fibers only in the interlobular stroma.
2. Tumors having areas with and areas without fibers; that is, a combination of groups 1 and 3. This group is subdivided into (*a*) tumors having a definite preponderance of fiberless areas; (*b*) tumors having areas with and areas without fibers in approximately equal numbers, and (*c*) tumors having a definite preponderance of areas containing fibers.
3. Tumors having, in all areas, fibers forming a network about individual tumor cells.

In the classification of tumors by fiber content, the malignancy of the tumor appears to be inversely proportional to the degree of intercellular invasion by argyrophil fibers.

The outstanding facts brought forward in their recent article are that there are still no deaths from tumors of the spindle cell subtype A or from tumors of group 3 in the classification according to fiber content and that the patient in every case in which no argyrophil fibers appeared among the tumor cells has died. Wilder and Callender concluded that the two classifications used in conjunction with each other definitely narrow the field of error in the prognosis of uveal melanoma.

SUMMARY

Melanin was present in each of the tumors examined.

Freedom from metastasis for the usual five year period is not a sufficient interval to determine malignancy. Metastasis after twenty-four

2. Callender, G. R., and Wilder, H. C.: Melanoma of the Choroid, Am. J. Cancer **25**:251, 1935.

years has been noted. In 1 of my cases, death from multiple metastasis occurred in the tenth year following enucleation.

Separation of the retina is a common complication of sarcoma of the choroid. The disturbance of vision which it sets up was what brought most of my patients to consultation. I should like to emphasize that a serous detachment of the retina may be the primary symptom also of metastatic carcinoma of the choroid. In a patient over the fortieth year a spontaneous detachment of the retina in a nonmyopic eye should be held in the greatest suspicion.

Malignant tumors of the uveal tract can be graded according to cellular morphologic structure. In Callender's first tabulation [1] and in the report of Terry and Johns [3] the mixed cell tumor appeared to be the most malignant. Wilder and Callender,[4] in their last report, said: "The epithelial group, with the increase in cases followed over five years, shows an increase in the percentage of metastatic deaths, and it is now placed ahead of the mixed-cell type in malignancy rating. In the classification of tumours by fibre content, malignancy of the tumour appears to be inversely proportional to the degree of intercellular invasion by argyrophil fibres." The value of grading tumors by cellular morphologic structure and by the presence or absence of argyrophil fibers can be determined only by further study and follow-up observation.

While in this small series the duration of observation has been insufficient to allow definite conclusions to be drawn, unquestionably the follow-up in these cases tends to verify the statement of Wilder and Callender [4] that the spindle cell (subtype A) tumor is relatively benign. In this series, observed over a period of sixteen years, there have been no deaths from this type of growth.

---

3. Terry, T. L., and Johns, J. P.: Uveal Sarcoma—Malignant Melanoma, Am. J. Ophth. **18**:903, 1935.

4. Wilder, H. C., and Callender, G. R.: Malignant Melanoma of the Choroid, Am. J. Ophth. **22**:851, 1939.

EXPANSION TENDENCY OF THE VITREOUS AND ITS p_H VOLUME CURVE

L. VON SALLMANN, M.D.
NEW YORK

Investigations made so far of changes in volume of the vitreous body in connection with different hydrogen ion concentrations were performed on dissected parts of the solid vitreous of the larger animals. This holds good both for the experiments of Baurmann,[1] who was the first to investigate this problem systematically, and for those of Duke-Elder,[2] Goedbloed [3] and others. The destruction of the vitreous body was carried out to an even greater extent in the studies of Salit and O'Brien [4] and others. The previous literature, beginning with Fischer's [5] well known investigations, comprises a large number of articles referring to the question of swelling of the vitreous and glaucoma. The technic described in the studies reported in these publications as well as in some later experiments was met by so much critical objection, however, that a description of this experimental work can be dispensed with.

The use of dissected parts of the vitreous to solve the question in hand might be justified if the vitreous could be considered a completely structureless gel, as it was described by Redslob,[6] Cattaneo,[7] Leplat,[8]

Supported by the Knapp Memorial Foundation.

From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology, Presbyterian Hospital.

1. Baurmann, M.: Untersuchungen über die Struktur des Glaskörpers bei Säugetieren, Arch. f. Ophth. **111**:352, 1923; Untersuchungen über die Eigenschaften des Glaskörpers des Tierauges, ibid. **114**:276, 1924.

2. Duke-Elder, W. S.: The Physico-Chemical Properties of the Vitreous Body, J. Physiol. **68**:155, 1929; The Vitreous Humor, Tr. Ophth. Soc. U. Kingdom **49**:83, 1929; The Nature of the Vitreous Body, Brit. J. Ophth., 1930, supp. 4, p. 1.

3. Goedbloed, J.: Studien am Glaskörper, Arch. f. Ophth. **132**:323, 1934; **133**:1, 1935; **134**:146, 1935; **137**:127, and 131, 1937.

4. Salit, P. W., and O'Brien, C. S.: The Behavior of the Vitreous Under Different Hydrogen and Hydroxyl Ion Concentrations: A Study in Vitro, Arch. Ophth. **5**:903 (June) 1931.

5. Fischer, M. H.: Augenquellung und Glaukom, Arch. f. d. ges. Physiol. **127**:1, 1909.

6. Redslob, E.: Contribution à l'étude de la structure du vitré, Ann. d'ocul. **164**:107, 1927; Le corps vitré, Paris, Masson & Cie, 1932; Le développement du corps vitré chez le poulet, Ann. d'ocul. **168**:29, 1931.

(Footnotes continued on next page)

Fracassi,[9] Slonaker,[10] Cowan and Fry [11] and others. Provided there is nothing but an ultramicroscopic structure with a changing density of the elements (fibrils [Baurmann and Thiessen;[12] Heesch;[13] Strömberg;[14] Duke-Elder] or sheets [Friedenwald and Stiehler [15]]) in various parts of the vitreous, a volumetric examination of the vitreous body in toto seems advisable. This demand is the more cogent if sufficient proof is given of the existence of a vitreous structure with a real Cloquet's canal, a membrane-like border layer and a framework of a certain architecture. The results obtained by Goedbloed and by Friedenwald and Stiehler in the field of ultramicroscopy and those obtained by Szent-Györgyi [16] in the field of histology may safely be considered such proof. Without underestimating the value of ultramicroscopic observations, the topographic features can hardly be measured by the examination of minute parts of the vitreous pressed into cuvettes, during which procedure a considerable deformation of the elements takes place. On the other hand, certain topographic aspects of the vitreous can be obtained by the histologic methods of Szent-Györgyi in a convincing way, despite the arguments raised against the application of histologic methods to the vitreous.[17] In view of these explanations it appears desirable to carry

7. Cattaneo, D.: Osservazioni sulla struttura del vitreo, Mem. d. r. Accad. naz. d. Lincei, Cl. di sc. fis., mat. e nat. **5**:53, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **28**:305, 1933.

8. Leplat, G.: Contribution à l'étude du corps vitré, Ann. d'ocul. **169**:531, 1932.

9. Fracassi, G.: Entwicklung und Morphologie des Glaskörpers beim Menschen und bei einigen Säugetieren, Arch. f. Ophth. **111**:219, 1923.

10. Slonaker, J. R.: The Development of the Eye and Its Accessory Parts in the English Sparrow, J. Morphol. **35**:263, 1921.

11. Cowan, A., and Fry, W. E.: The Hyaloid Membrane of the Vitreous, Am. J. Ophth. **15**:428, 1932.

12. Baurmann, M., and Thiessen, A.: Die Struktur im Glaskörper des Auges, Nachr. v. d. Gesellsch. d. Wissensch. zu Göttingen, Math.-physik. Kl., 1922; cited by Goedbloed.[3]

13. Heesch, K.: Ultramikroskopische Untersuchungen über die Struktur im Glaskörper des Tierauges, Arch. f. Augenh. **97**:534, 1926; Untersuchungen über den Zusammenhang zwischen der ultramikroskopischen und der mikroskopischen Fadenstruktur des Glaskörpers, ibid. **98**:129, 1928; Zur Frage des Zusammenhanges der ultramikroskopischen Struktur des Glaskörpers mit den Spaltlampenbefunden, ibid. **98**:121, 1928; Die Anatomie des Glaskörpers, ibid. **100-101**:680, 1929.

14. Strömberg, E.: Zur Frage nach dem Bau des Glaskörpers, Acta med. Scandinav. **57**:365, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **27**:44, 1932.

15. Friedenwald, J. S., and Stiehler, R. D.: Structure of the Vitreous, Arch. Ophth. **14**:789 (Nov.) 1935.

16. Szent-Györgyi, A.: Untersuchungen über den Bau des Glaskörpers des Menschen, Arch. f. mikr. Anat. **90** (pt. 1):324, 1917.

17. The interesting experiments of Friedenwald and Stiehler, who applied a modified frozen technic (used in other anatomic fields) for the histologic examina-

out the volumetric measurements of the vitreous without destroying its fibrillar framework and anatomic configuration.

The volume curve of Baurmann and Thiessen, Duke-Elder and Goedbloed shows a steady decrease of the volume in all ranges of p_H. This decrease is relatively small in the ranges of the weak acid and the weak alkaline p_H and in physiologic solution of sodium chloride. In the higher alkaline and acid ranges the decrease in volume is particularly great; in the highest acid ranges it is somewhat smaller. In the milieu of physiologic solution of sodium chloride the vitreous diminishes continuously in volume. Goedbloed stated that the vitreous cannot regain its volume once it has lost it and therefore is not elastic. Later he confined his statement to solutions containing more than 10 milliequivalents of neutral salt. It could not be proved, therefore, by experiments in vitro that the vitreous had any expansion tendency and turgescence pressure under physiologic conditions. So the explanations of the qualities of the vitreous in vivo have been of restricted applicability in both normal and abnormal conditions. It is widely accepted that the main part of the humor of the vitreous is capillary fluid and that only a very small amount is colloidally bound to the vitreous skeleton as hydration water. The capillary fluid seems to escape readily in an injury of the vitreous. If the vitreous is removed in toto from its surrounding coats, this escape will occur, especially on the vitreous base and at the area martegiani.

In the following experiments an attempt was made to prevent this escape of fluid. Pigs' eyes were selected as the objects of examination because in consistency their vitreous resembles that of the human eye more than does the vitreous of the eyes of horses and cattle. The vitreous was examined in toto and in a great number of experiments with the nerve head and ciliary body in place. These experiments were extended to human eyes removed three hours after death in order to investigate the changes in volume and to compare these with the results obtained with pigs' eyes.

TECHNIC OF EXPERIMENTS ON PIGS' EYES

Fresh pigs' eyes were prepared in two ways. In the first group of experiments the vitreous was completely isolated. This was easily done except for the fovea patellaris, the vitreous base and the area martegiani. In these places injury was unavoidable as a matter of course. In the second group, the ciliary body, the retina (including the nerve head) and the posterior lens capsule were left in place. To achieve this result a crucial incision through the cornea was elongated by scissors into the sclera, with careful avoidance of any lesion of the ciliary body at the scleral spur. A circular incision severed the ciliary body from its insertion. After

tion of the vitreous, may strengthen the belief of those who value histologic methods applied to the vitreous. Rigid opponents may argue that the new method is only another way to denature and fix plasma and tissue structures, with the same possibilities of producing artefacts.

the crucial incision had been extended to the posterior third of the sclera and the lens, removed with the exception of the posterior capsule, the choroid was opened and incised around the equator. The next step was the removal of the choroid and scleral sectors in the posterior half, a thin disk of nerve tissue being left in connection with the intact retina. The anterior half of the choroid and the iris were eventually cut off. A few artificial holes in the retina did not make much difference in the value of the preparation provided the vitreous base and the region of the nerve entrance had not been injured. To prevent an extensive rupture of the retina, it was advisable to complete the procedure under physiologic solution of sodium chloride. The vitreous body, protected in this way from the uncontrolled escape of its fluid was then supported by a medium-sized mesh net of hair or fine silk in the form of a bag and placed in the apparatus for volumetric measurement. The entire procedure of making up the preparation required about ten minutes. Although damage to the structure of the vitreous body could not be completely avoided, owing to a certain pressure in manipulation, it was certainly much less serious than the destruction entailed by other methods. The volume was measured in a small beaker provided with a narrow outflow tube at a distance of 1.5 cm. from the rim. The volumometer, placed on a horizontal base, was filled to the level of the aperture, and into this fluid the preparation in the hair net was freely suspended. The overflowing fluid displaced by the preparation was measured in a graduate with a narrow neck and a bulbous base. A second measurement was made by means of Goedbloed's apparatus. It gave more accurate results in general, so that in later series this instrument, somewhat modified, was used exclusively. After the determination of the volume the vitreous preparations, supported by hair nets, were suspended in vessels containing the solutions of different p_H. The measurements were repeated after twelve, twenty-four, forty-eight and, occasionally, seventy-two hours. The transference of the vitreous from one vessel to the other by means of the hair net bag reduced damage to the preparation as far as possible. Control experiments with the hair net bag containing the retina without the vitreous proved that changes in volume could not be attributed to causes extraneous to the vitreous. After forty-eight hours the preparations showed signs of autolysis, so most of the experiments were not carried beyond that point.

EXAMINATION OF ISOLATED PIGS' VITREOUS IN SOLUTIONS OF POTASSIUM HYDROXIDE AND HYDROCHLORIC ACID IN DISTILLED WATER

The results of experiments with pigs' vitreous isolated but not protected resemble the volumetric curve for the vitreous of cattle and horses, published by Baurmann and Duke-Elder. A decrease in volume was evident in all the solutions examined, but the maximal decrease was manifest at p_H 2 and the minimal decrease at p_H 10. The changes in volume in solutions at a p_H of 9 and 5 respectively did not exceed a small percentage. The figures showing the volume in the respective solutions after forty-eight and seventy-two hours gave the same form of curve as the one obtained after twenty-four hours except that they lay in lower levels. The figures on the chart represent the average of 5 experiments of a series (chart 1).

EXAMINATION OF PIGS' EYES WITH PROTECTED VITREOUS BASE AND AREA MARTEGIANI IN SOLUTIONS OF POTASSIUM HYDROXIDE AND HYDROCHLORIC ACID IN DISTILLED WATER

When the escape of the vitreous fluid at the vitreous base and the area martegiani was avoided, a marked difference in the character of the curve could be observed. The volume of the preparations with an uninjured and protected vitreous showed an increase after twenty-four hours in all except the strongly acid and strongly alkaline ranges. The maximal swelling occurred at p_H 11 and the second peak at p_H 3. At p_H 12 the liquefaction of the vitreous was so advanced that the volumetric

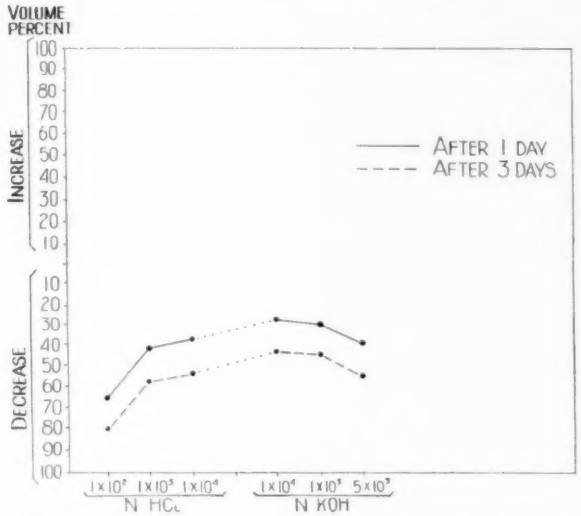


Chart 1.—Pigs' vitreous (without retina) in solutions of hydrochloric acid and potassium hydroxide in distilled water.

methods used in these experiments did not give satisfactory or reliable results. The maximal shrinkage occurred at p_H 2. In the two following days the volume decreased but the type of curve did not change. Again the figures of the curve represent the average of 5 experiments of a series (chart 2).

EXAMINATION OF PIGS' EYES WITH PROTECTED VITREOUS BASE AND AREA MARTEGIANI IN ISOTONIC SOLUTIONS

(*a*) *In Physiologic Solution of Sodium Chloride and Ringer's Solution.*—The examinations of vitreous preparations in physiologic solution of sodium chloride and in Ringer's solution of neutral reaction are represented in chart 3. The condition of the eye before preparation seems to be of great importance, and it may vary in accordance with the length of time after slaughter, the temperature and the age and

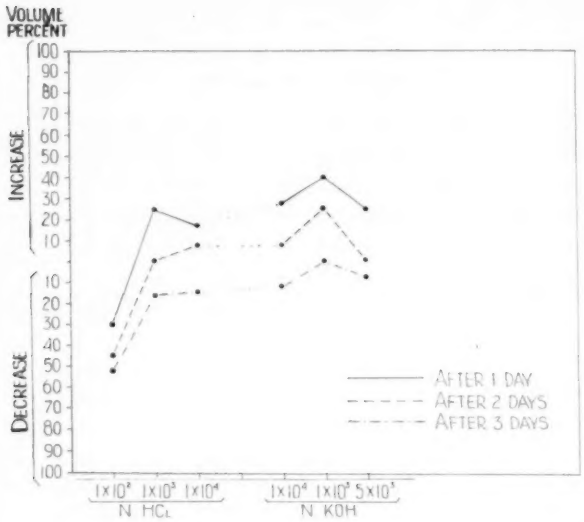


Chart 2.—Pigs' vitreous (with retina) in solutions of hydrochloric acid and potassium hydroxide in distilled water.

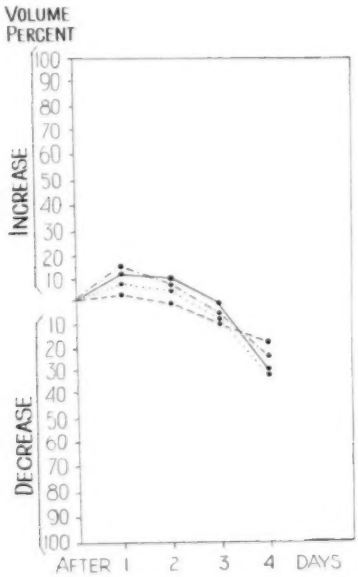


Chart 3.—Pigs' vitreous (with retina) in 0.9 per cent sodium chloride solution.

species of the animal. The procedure of preparation may also affect the results. Thus, the amount of pressure exerted on the eyeballs during preparation will differ, and a defect in the retina is often unavoidable. The procedure of measuring includes several changes of the preparation to and from the volumometer, and despite the care taken to make the change in the same length of time the quantity of fluid clinging to the vitreous and to the veil may vary. Although the sources of error were reduced as much as possible in our experiments, they must be considered, since they may cause differences of 5 per cent in either direction.

(*b*) *In Isotonic Buffered Solutions.*—To attempt a somewhat closer approximation to physiologic conditions, the experiments on the vitreous of pigs' eyes were continued in buffered solutions with an osmotic pressure equal to that of 0.9 per cent of sodium chloride. In these experiments the p_H ranges between 10 and 6 were also considered. Solutions with a p_H of 4 to 8 were prepared with sodium acetate–barbital as a buffer. The solutions with p_H 11, 10, 9, 3 and 2 were prepared with sodium hydroxide and hydrochloric acid respectively, with aminoacetic acid as a buffer. After the experiments had been finished, the p_H of the solutions was checked in two series of experiments.[18]

First Series		Second Series	
p_H Before Use	p_H After Use	p_H Before Use	p_H After Use
4.03	4.13	4.0	4.09
5.08	5.16	5.1	5.19
5.98	6.18	6.0	6.14
7.02	7.03	7.0	6.90

The readings differed from those obtained with the original solutions to a very small degree. The p_H figures marked on the curve were within 0.03 of the value as measured by a glass electrode at 28 C. They were modified to isotonicity with 0.154 normal sodium chloride.

The figures of this curve again represent the average of 5 experiments in a series. The curve based on the measurements after forty-eight hours is almost parallel to the one obtained after twenty-four hours but lies below it (chart 4).

The changes in volume in the p_H ranges between 10 and 4, which alone could be of any practical interest, were very moderate. The maximal swelling, of 16 volumes per cent, occurred at p_H 7. On the alkaline side, at p_H 8, the increase was slightly less (11 per cent), and on the acid side, at p_H 6, the increase was also less (12 per cent). Beyond p_H 10 a steep increase in volume corresponds to the findings in the experiments with potassium hydroxide and hydrochloric acid in distilled water; at p_H 11 the increase was 50 per cent of the original

18. Prof. W. J. V. Osterhout and his assistants, of the Rockefeller Institute for Medical Research, prepared and checked the solutions of different p_H and also gave valuable advice.

volume. From p_H 4 the volume decreased greatly in the strongly acid ranges. On account of the possible errors of the method used, it is advisable to be cautious in drawing specific conclusions from these results. But it must be stated that the increase in volume in weak alkaline or acid solutions was less than that obtained with neutral solutions. These results are contrary to the findings of different authors based on other technics and on the vitreous of horses and cattle. Especially the p_H curve of Baurmann with buffered nonisotonic solutions shows less deturgescence in the weak alkaline ranges. The main difference between the curve in p_H solutions made up in distilled water and that in isotonic buffered solutions is the absence of elevation at p_H 3.

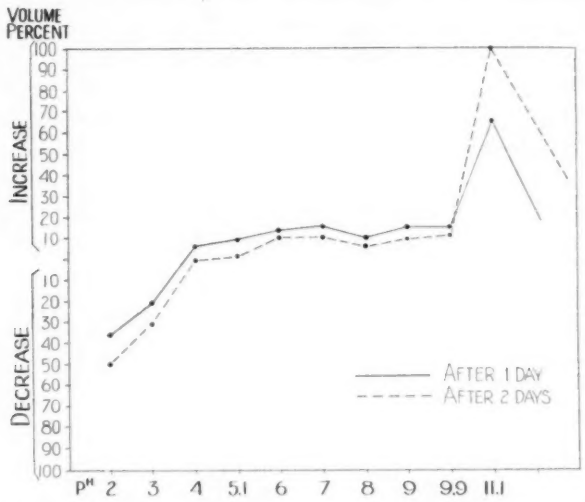


Chart 4.—Pigs' vitreous (with retina) in isotonic buffered solutions of hydrochloric acid and potassium hydroxide.

EXPERIMENTS ON HUMAN EYES

The influence of p_H of the milieu on the human vitreous has not been studied up to the present time. One reason for this may be the difficulty involved in obtaining the vitreous of human eyes before serious postmortem changes have occurred. Another reason may be that the experimental technic used on the vitreous of horses and cattle by other authors cannot be used on that of the human eye because of the consistency of the human vitreous. For the following experiments the eyes were removed three to four hours after death. The vitreous, covered with the posterior lens capsule, ciliary body and retina, was prepared very carefully in the usual way. The retina of an old person is often more fragile, especially in the macular area, and small tears of the retina in this region may interfere with the results of the experiments if the vitreous is liquefied or detached. The inner part of the nerve head was left in place. Occa-

sionally the lens was removed in the capsule. Such a preparation must be handled very cautiously to avoid rupture of the limiting layer on the anterior surface of the vitreous.

The eyes were taken from persons who had died at an age of 32 to 76 years. Thirty eyes from 15 persons were used. With few exceptions the eyes were normal according to the histories and objective observations at postmortem examination. The eyegrounds, which could be easily examined with a loupe, also did not show any pathologic changes. The observations on 1 cadaver with absolute glaucoma of one eye and a normal other eye and on a cadaver with senile cataract will be reported separately. The final condition before death, the lethal disease and the age are possible factors of some influence on the physicochemical qualities of the vitreous.

The influence of different p_H ranges was studied in solutions with distilled water corresponding to those used in the experiments on pig's eyes and in the examinations of the eyes of horses and cattle used by other authors. The experiments could not be extended to isotonic buffered solutions on account of the limited number of eyes obtainable under suitable conditions. The solutions of different p_H were used only in 1 or 2 cases, with the exception of the solution 1×10^{-3} normal potassium hydroxide (4 cases). Like the preparations of pigs' vitreous, the preparations of human vitreous showed a tendency toward expansion (chart 5). A comparison of the volume curves of pigs' eyes and the figures obtained mostly from single experiments on human eyes does not reveal any essential differences. In physiologic solution of sodium chloride or Ringer's solution the vitreous preparation increased in volume from 15 to 19 per cent. The ages of the persons from whom these eyes were taken (32, 41 and 61 years) did not appear to make any appreciable difference. This can also be stated in regard to the experiments with different potassium hydroxide and hydrochloric acid solutions made up in distilled water. The greatest expansion (more than 50 per cent) was observed in persons older than 60 years. The vitreous of one eye of the oldest person (76 years) increased its volume 52 per cent; this is rather unexpected because of the generally advanced liquefaction of the vitreous at that age.

Special consideration may be given to a case of absolute primary glaucoma of the left eye. The patient was seen ante mortem. The left eye had been blind for several years. The eye was white, the cornea somewhat cloudy, the iris atrophic and the pupil dilated and round; because of a silky cataract, the eyeground could not be examined. Tension was $+ +$. The other eye seemed normal. In the preparation of the left eyeball (post mortem) a broad anterior peripheral synechia, an atrophic nerve head with a total deep excavation and a few hemorrhages in the retina were revealed. The right eye showed some peripheral anterior synechiae. The vitreous preparations of both eyes were

carefully made without injury to the protecting membranes and were kept in the same fluid, i. e., 3×10^{-3} normal potassium hydroxide in distilled water. The swelling of the vitreous of the glaucomatous eye (34 per cent) was remarkably less than that of the normal one (52 per cent). In the following days the volume of the vitreous of the glaucomatous eye did not decrease below the original volume in an observation period of ninety-six hours. At that time it was still 13 per cent larger than it had been originally. The other vitreous decreased in volume as usual until it lost 79 per cent of its original volume after ninety-six hours. Despite the singularity of the observation, it is reported here because of the rare possibility of examining in vitro the vitreous of a person with one normal and one glaucomatous eye.

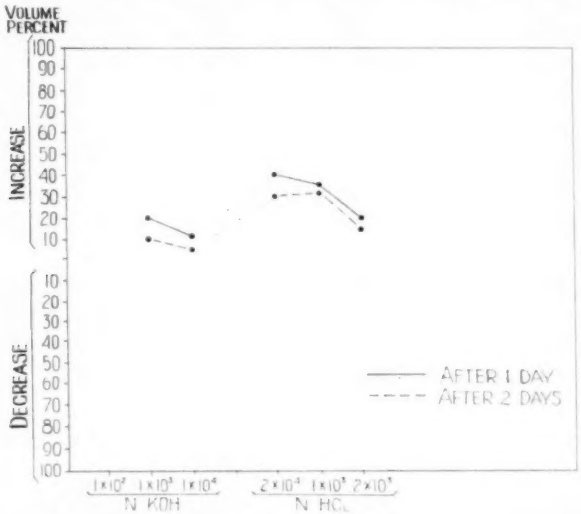


Chart 5.—Human vitreous (with retina) in solutions of hydrochloric acid and potassium hydroxide in distilled water.

Two subjects with highly liquefied vitreous have shown that the tendency to expand is lessened or lost with liquefaction. Cadaver 16 (aged 69 years), with a small defect in the retina and limiting layer, had a liquefied vitreous. The 13.5 per cent increase in volume was much less than the average 39 per cent increase in 3 other experiments with the same solution of 1×10^{-3} normal potassium hydroxide. Still more convincing are the results with cadaver 14. The right eye had a mature senile cataract and the left eye an incipient one. In the preparation of the right eye the retina and the limiting membrane were accidentally injured in the macular area. Despite the minuteness of the defect, fluid escaped from the vitreous in such an amount that the preparation collapsed completely. The vitreous of the left eye was then prepared very carefully, and any lesion of the protecting membrane was

avoided. Examination of this uninjured vitreous in a solution of 1×10^{-5} potassium hydroxide in distilled water revealed no change in volume after twenty-four hours and a decrease of 10 per cent after forty-eight hours. The lack of expansion could not be attributed to the p_H of the solution in view of the results of other experiments. It may be concluded, therefore, that extreme liquefaction of the vitreous inhibits the tendency to expand.

COMMENT

In review, by preventing the uncontrolled escape of fluid from the vitreous, a definite swelling of the vitreous was demonstrated; the p_H curve thus obtained is based, therefore, on an actual increase in volume. Previous, aforementioned authors deduced a p_H curve from the different degrees of volume loss and interpreted these figures as indicating a relative swelling in comparison to each other. Their volume curve differs from mine in several ways. The most important difference is found in the slightly alkaline and acid isotonic solutions (p_H 6 and 8) in which the swelling was less than that at a p_H of 7, contrary to the curves of Baurmann and others, who found the least volume decrease (interpreted as the maximal swelling) in a weakly alkaline solution. The experiments on the vitreous of human eyes could not be extended to isotonic solutions, but the similar behavior of pigs' vitreous and human vitreous in solutions of varying p_H made up in distilled water and in neutral physiologic solution of sodium chloride indicates that the results of the experiments on pigs' vitreous in isotonic solutions may be applied to the vitreous of the human eye.

The chemical process of proteolysis of the vitreous directly associated with liquefaction and degeneration was studied in vitro by Krause.[19] But very little is known of the connection between the expansion tendency and liquefaction. This question is closely allied to the problem of expansion per se.

The moderate swelling of the vitreous in saline solution (0.9 per cent sodium chloride of neutral p_H) or in Ringer's solution may be explained in two ways: It cannot be excluded that osmotic processes take place, since they depend also on differences of partial salt concentration. On the other hand, pressure exerted on the eye during enucleation and especially during the preparation of the vitreous specimen reduces the volume by the escape of fluid from the vitreous. A certain degree of elasticity, inherent in the framework, could be responsible, therefore, for the expansion to the original volume. The increase obtained in these experiments contradicts Goedbloed's statement that the shrunken vitreous does not regain its volume in a physiologic milieu.

19. Krause, A. C.: The Chemistry of the Vitreous Humor: I. The Chemical Composition of the Proteins, Arch. Ophth. **11**:960 (June) 1934; II. Proteolysis, ibid. **11**:964 (June) 1934.

The experiments prove that the vitreous has a tendency to expand as expected according to clinical experiences; it retains its volume in vitro for about twenty-four hours after enucleation. It cannot be decided whether this expansion produces a volume in excess of the original volume. The decrease in volume in the following days is probably caused by autolytic decomposition of the simple protein substances and disintegration of the protecting structures of the preparation and is unrelated, therefore, to the problem in question.

The much greater swelling of the vitreous preparations in hypotonic solutions resembles the results of Goedbloed's experiments with pieces of vitreous treated for several days in distilled water. Goedbloed expressed the opinion that this extreme desalination causes increased capillarelectric activity of the fibrillae, which consist of protein substances, and thus the meshwork plays the main role in the swelling. An increased repulsion of the fibrillae may cause an enlargement of the intrafibrillary meshes and a simultaneous absorption of fluid from the surrounding milieu. The absorption of fluid by the dissolved mucoprotein is without doubt of minor importance.

In the aforementioned observations on liquefied vitreous the conditions were, however, different from those in the experiments of Goedbloed. The technic applied to human eyes, like that applied to pigs' eyes, did not give an extreme desalination, but it may be supposed that a partial desalination may have a similar result. The absence of expansion in the eye with an entirely liquefied vitreous, in contrast to the swelling in other eyes, speaks for the fact that the framework has an active part in the process of swelling.

SUMMARY

1. By using preparations of the vitreous of pigs' eyes with protection of the vitreous base and of the area martegiani it could be demonstrated in vitro that the vitreous has a tendency to expand and that under physiologic conditions it can regain its volume (if this is diminished) and retain it temporarily.

2. The p_H volume curve with buffered isotonic solutions showed a steep increase in the strongly alkaline ranges and a steep decrease in the strongly acid ranges. In both weakly alkaline and acid ranges, however, the moderate swelling was less than that observed at p_H 7.

3. Studies on the vitreous of human eyes removed three hours after death revealed that it reacted essentially in the same way as the vitreous of pigs' eyes in these experiments.

4. The experiments in vitro did not give any indication of a possible correlation between changes of p_H within physiologic limits and increased tension of the eyeball.

5. The vitreous of the human eye when entirely liquefied seems to lose its tendency to expand.

OCULAR LYMPHOGRANULOMA VENEREUM

JOHN P. MACNIE, M.D.
NEW YORK

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum has been defined by Stannus [1]—who called it the sixth venereal disease—as a human contagious disease which is acquired venereally, is possibly more common in warm climates than in cold and is due to an ultramicroscopic filtrable virus communicable to certain experimental animals. Although the genital tract is the usual portal of entry, extragenital infections have occurred, purposefully (Levaditi, Marie and Lépine [2]) and accidentally (Appelmans [3]). With the exception of these rare cases, the disease may be said to develop in three stages (Coutts [4]).

Stages of the Disease.—First Stage: After an incubation period varying from a few days to two weeks, the initial lesion develops as a small, insignificant, often transitory, ulcerative or herpetiform inoculatory lesion on the genitalia.

Second Stage: Ten days to several weeks or even months after the appearance of the initial lesion, a characteristic subacute or chronic inflammatory neoformative reaction develops in the regional lymphatic glands and adjacent connective tissue and usually progresses to suppuration. In the female, the perirectal and retroperitoneal glands are involved more frequently than the inguinal glands, and the disease is much more likely to progress to a third stage. In the male the disappearance of the inguinal buboes usually marks the end of the disease, and in the majority of cases no serious sequelae result (D'Aunoy and von Haam [5]).

Presented as a candidate's thesis to the American Ophthalmological Society, 1940.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

1. Stannus, H. S.: A Sixth Venereal Disease, London, Baillière, Tindall & Cox, 1933.

2. Levaditi, C.; Marie, A., and Lépine, P.: Compt. rend. Soc. de biol. **107:** 1496, 1931.

3. Appelmans, M.: Ophthalmologica **96:**321, 1939.

4. Coutts, W. E.: J. Trop. Med. **39:**13, 1936.

5. D'Aunoy, R., and von Haam, E.: Venereal Lymphogranuloma, Arch. Path. **27:**1032 (June) 1939.

Third Stage: In some cases the disease progresses to a third stage, which is characterized by hypertrophic ulceration of the pudenda (referred to as esthiomene by many authors) or by inflammatory stricture of the rectum. Lesions of the anus, perineum or rectum may be associated with esthiomene.

Constitutional Symptoms.—Associated constitutional symptoms may include lassitude, prostration, fever, sweats, anorexia, loss of weight, rheumatic conditions and cutaneous reactions (Stannus [1]). These manifestations and the occurrence of remote lesions point to a generalized infection (von Haam and D'Aunoy [6]), but the rarity of the latter in comparison with the symptoms localized in the genital area suggest that in most instances the virus is neutralized or destroyed except in relation to the local lesions.

Other Names for Lymphogranuloma Venereum.—It was not until 1913, when Durand, Nicolas and Favre [7] published a description of the disease, in which they associated its various manifestations and differentiated it from syphilis and tuberculosis, that a common cause was established for a number of apparently unrelated symptoms. Prior to this event the lesions had been designated variously as chancre lymphogranulomateux, bubon d'emblée, pestis minor, climatic bubo, ulcus rodens vulvae, syphilome anorectale and ulcus callosium stenoticans recti.

Durand, Nicolas and Favre called their syndrome lymphogranulomatose inguinale subaigue, from which the terms lymphogranuloma inguinale and lymphogranulomatosis inguinalis were later derived (von Haam and D'Aunoy [6]). In Germany and Italy the name poradenitis (Fiessinger [8]) is used, and in the American literature lymphopathia venereum was advocated by Sulzberger and Wise.[9] In Europe the term Nicolas-Favre disease has come into use in recognition of the physicians who first described the condition as a clinical entity.

Distribution.—Lymphogranuloma venereum seems to occur more frequently in males than in females and, according to Martin,[10] more often in Negroes than in white persons. It is probably much more common than is generally realized. There are only a few places in the world in which the public health regulations require that it be reported; this is the case in the United States only in Alabama, Cali-

6. von Haam, E., and D'Aunoy, R.: Am. J. Trop. Med. **16**:527, 1936.

7. Durand, M.; Nicolas, J., and Favre, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **35**:274, 1913.

8. Fiessinger, N.: Rev. gén. de clin. et de thérap. **39**:162, 1925.

9. Sulzberger, M. B., and Wise, F.: Lymphopathia Venereum (Lymphogranulomatosis Inguinalis of Nicolas, Favre and Durand), J. A. M. A. **99**:1407 (Oct. 22) 1932.

10. Martin, C. F.: Stricture of Rectum: Some of Its Problems, J. A. M. A. **101**:1550 (Nov. 11) 1933.

fornia, Illinois and Washington (Nelson [11]). Hellerström and Wassén [12] have found the disease in Europe, along the coasts of Africa, in North and South America and in Australia. They stated the belief that it was carried to Europe by soldiers and sailors who had visited tropical countries, where it is common. In a review of a small portion of the literature of the years 1930-1936, Bacon [13] found 3,977 cases reported.

Etiology.—Early attempts to isolate or cultivate the causal agent of lymphogranuloma venereum from the pus of the involved inguinal glands were unsuccessful. In 1931 Hellerström and Wassén [14] transmitted the disease to monkeys by intracerebral injection of bubonic material, and later, simultaneously with Levaditi, Ravaut, Lépine and Schoen,[15] they demonstrated an infective virus in filtrates from lesions produced in this way. A virus showing identical biologic and physical properties was isolated from a primary human lesion by Löhe, Rosenfeld, Schlossberger and Krumeich [16] in 1933, from climatic buboes by Findlay [17] in 1933 and from tissue taken from inflammatory stricture of the rectum by Laederich, Levaditi, Mamou and Beauchesne [18] in 1932. These findings have been confirmed by other workers, and the virus etiology of the disease is now generally accepted.

Properties of the Virus.—The filtrability of the virus of lymphogranuloma venereum has been established, but successful filtration cannot always be accomplished, on account of the difficulty of controlling such factors as hydrogen ion concentration, the concentration of the virus in the emulsion and the adsorption losses in the filter. The virus is comparable in size to the virus of vaccinia, measuring between 0.125 and 0.175 microns (Broom and Findlay [19]). It is resistant to cold and to freezing, remaining virulent for twenty-three days at 4 C. and for thirty days in a frozen state, but it is inactivated by heating to 56 C. for thirty minutes (Levaditi, Ravaut, Lépine and Schoen [15]).

---

11. Nelson, N. A.: Lymphogranuloma Inguinale, in Harvard School of Public Health, Symposium: Virus and Rickettsial Diseases, with Especial Consideration of Their Public Health Significance, Cambridge, Mass., Harvard University Press, 1940.

12. Hellerström, S., and Wassén, E.: Epidemiology and Etiology of Lymphogranuloma Inguinale, Paris, Masson & Cie, 1934.

13. Bacon, H. E.: M. Rec. **143**:517, 1936.

14. Hellerström, S., and Wassén, E.: Compt. rend. Soc. de biol. **106**:802, 1931.

15. Levaditi, C.; Ravaut, P.; Lépine, P., and Schoen, R.: Ann. Inst. Pasteur **48**:27, 1932.

16. Löhe, H.; Rosenfeld, H.; Schlossberger, H., and Krumeich, R.: Med. Klin. **29**:577, 1933.

17. Findlay, G. M.: Tr. Roy. Soc. Trop. Med. & Hyg. **27**:35, 1933.

18. Laederich, L.; Levaditi, C.; Mamou, H., and Beauchesne, H.: Bull. et mém. Soc. méd. d. hôp. de Paris **56**:1072, 1932.

19. Broom, J. C., and Findlay, G. M.: Brit. J. Exper. Path. **17**:135, 1936.

Cultivation of the virus in vitro has been accomplished with methods of tissue culturing by numerous investigators (Sanders [20] and Gey and Bang [21]). Tamura [22] inoculated tissue-Tyrode medium with material from involved glands and demonstrated granulocorpuscles with Giemsa stain. These were similar to the elementary bodies of other virus diseases. Gamna [23] described small bodies less than 3 microns in size found in material from infected glands.

In large mononuclear cells from infected tissue-culture material Miyagawa, Mitamura, Yaoi, Ishii, Okanishi, Goto and Shimizu [24] demonstrated minute bodies which they identified with the virus. Findlay, Mackenzie and MacCallum [25] found in infected material from mice, large and small granular forms closely resembling the large and small forms of the virus of psittacosis and postulated an intracellular developmental cycle from large to small forms. They suggested further that unsuccessful filtration attempts may be related to the occurrence of these large forms, which will not pass the usual filters.

More recently Gey and Bang [21] have described inclusion bodies, consisting of granulocorpuscles located in cytoplasmic vacuoles, in infected tissue culture cells. Sanders,[20] on the other hand, failed to find inclusion bodies in tissue cultures of infected mouse brain.

Schoen [26] found granulocorpsucles consistently in the central nervous systems of white mice and in the inflammatory nodules of guinea pigs which had been infected with the virus.

Immunology.—It is not known whether there is an immunity, either natural or acquired, to lymphogranuloma venereum. Its more frequent occurrence among Negroes is probably due to their social and unhygienic habits (von Haam and D'Aunoy [6]). In 1925 Frei [27] discovered that a specific cutaneous reaction could be produced in patients with the disease. He removed pus from buboes of patients with the disease and diluted it. After sterilization by fractional heating, 0.1 cc. of this material was injected intradermally into a person affected or known to have been affected with lymphogranuloma venereum. A marked induration with erythema, which reached a maximum in forty-eight hours, developed at the site of the injection. This procedure is now designated as the Frei test. Frei stated that it was accurate in from 90 to 95 per cent of cases.

20. Sanders, M.: J. Exper. Med. **71**:113, 1940.
21. Gey, G. O., and Bang, F. B.: Bull. Johns Hopkins Hosp. **65**:393, 1939.
22. Tamura, J. T.: J. Lab. & Clin. Med. **20**:393, 1935.
23. Gamna, C.: Arch. di pat. e clin. med. **3**:305, 1924.
24. Miyagawa, Y.; Mitamura, T.; Yaoi, H.; Ishii, N.; Okanishi, J.; Goto, T., and Shimizu, S.: Jap. J. Exper. Med. **14**:207, 1936.
25. Findlay, G. M.; Mackenzie, R. D., and MacCallum, F. O.: Tr. Roy. Soc. Trop. Med. & Hyg. **32**:183, 1938.
26. Schoen, R.: Ann. Int. Pasteur **62**:260, 1939.
27. Frei, W.: Klin. Wchnschr. **4**:2148, 1925.

It is believed that there are numerous strains of the virus, but whether different strains produce different manifestations is not known (Coutts [4] and von Haam and D'Aunoy [6]).

Transmission to Animals.—White mice, certain species of monkeys (Macacus synomolgus, Hapale penicillata and the baboon) and ferrets are highly susceptible to the virus of lymphogranuloma venereum. Dogs, cats and guinea pigs, on the other hand, are difficult to infect, and rabbits, sheep and calves are even more resistant.

The most effective route of infection is the intracerebral. Inoculation by this route results in meningoencephalitis, which is fatal to many animals. That the infection spreads from the cerebral focus has been established by Levaditi, Ravaut, Lépine and Schoen,[28] who found virulent material in the liver, spleen, kidney, bone marrow and lymph glands (but not in the blood) which had been removed just before the death of an infected monkey. Subsequently, Levaditi and Reinié [29] decided that the virus after intracerebral inoculation into the monkey was not found free in the blood plasma but was attached to the leukocytes and lymphocytes. Meningoencephalitis, in turn, may result from intraperitoneal inoculation if at the same time the brain has been traumatized by the injection of a sterile starch solution (Findlay [17]). Von Haam and D'Aunoy [6] concluded that the dissemination of the virus in the body of the experimentally infected animals apparently depended on the route of inoculation; intracerebral and intraperitoneal injection usually lead to a generalized infection, while subcutaneous and preputial injection seldom produce more than infection of the regional lymph glands.

Pathology.—First Stage: In the ulcerative type of primary lesion there is localized necrosis of the epithelium and underlying connective tissue with proliferation at the borders, and the surrounding lymph vessels are dilated and filled with endothelial cells. The herpetiform type shows hyperplasia of the stratum granulosum with intraepithelial edema, and there is dense infiltration with small and large round cells and neutrophilic leukocytes in the stratum mucosum (D'Aunoy and von Haam [5]).

Second Stage: The inguinal buboes show enlarged glands with plastic periadenitis. Small abscesses develop, enlarge, become confluent and finally reach the surface through sinuses. Histologically the lesion shows proliferation of the endothelial cells lining the lymph spaces of the gland; mononuclear cells form nodules, the centers of which become necrotic when polymorphonuclear leukocytic invasion occurs. Healing is effected by fibrosis.

28. Levaditi, C.; Ravaut, P.; Lépine, P., and Schoen, R.: Compt. rend. Soc. de biol. **107**:959, 1931.

29. Levaditi, J., and Reinié, L.: Compt. rend. Soc. de biol. **118**:123, 1935.

Third Stage: Involvement of the regional lymph glands follows the initial lesion, and the site of these glands influences the future course of the disease. When the activity of the lymph glands persists, chronic edema and sclerosing fibrosis develop in the subcutaneous and submucous tissues, and there may be induration and enlargement of the affected parts. The covering epithelium suffers from insufficient circulation, and ulceration occurs. These changes are observed earlier in the rectum, since mucous membrane is more sensitive than skin to changes in the underlying tissues. Secondary infection invading such ulcerated areas establishes foci of infection, which in turn contribute to the chronic, progressive nature of the lesions in which they occur.

The histologic picture of these chronic lesions is not characteristic and provides no such basis for diagnosis as that found in the histologic picture of the acute bubo. The essential changes in rectal stricture are destruction and ulceration of the mucosa, infiltration of the muscular layer by miliary accumulations of lymphocytes and plasma cells, dilatation of the lymphatics and perilymphatic infiltrations and endolymphangitis (Lichtenstein [30]). The sclerosing process may extend far into the periproctic tissue. Adhesions may fix the sigmoid and rectum to the wall of the pelvis and neighboring organs, and a picture resembling chronic pelvic inflammatory disease may result.

D'Aunoy and von Haam [5] reported the case of a woman examined in their laboratory by Schenken. She had suffered for some time from inflammatory stricture of the rectum and was admitted to the hospital with symptoms of meningeal irritation, which were ascribed to pellagra, a frequent complication of stricture of the rectum. Autopsy and histologic examination revealed a diffuse meningeal reaction with lymphocyte and plasma cell infiltration and localized areas of superficial necrosis. Intracerebral inoculation into white mice of emulsions of material from the woman's brain produced symptoms of lymphogranuloma venereum encephalitis. The recovered virus was passed through the brains of several generations of white mice, and antigens prepared from them gave positive cutaneous reactions in patients known to have lymphogranuloma venereum.

Meningoencephalitis: Pathologic examination of infected mouse brain reveals a dense infiltration of the meninges of the brain, occasionally of the meninges of the upper part of the cord, and of the brain itself. Neutrophilic leukocytes, large and small mononuclear cells and plasma cells, arranged in cell nests around the smaller vessels, give rise to the so-called "lymphomas," which are fairly characteristic (D'Aunoy and von Haam [5]).

30. Lichtenstein, L.: Am. J. Surg. **31**:111, 1936.

Differential Diagnosis.—The inguinal adenitis of lymphogranuloma venereum may be confused with that of chancroid, syphilis, tuberculosis, malignant tumor, Hodgkin's disease, bubonic plague, tularemia and pyogenic infections. The lesions of the third stage must be differentiated from granuloma inguinale, chancroid, cancer, syphilis, tuberculosis, dysentery and ulcerative colitis.

The reliability of the Frei test as a diagnostic sign was found to be very high by D'Aunoy and von Haam,[5] who stated that it gave correct results in 98.1 per cent of a series of 500 patients with clinical lymphogranuloma venereum and over 800 controls. The activity of the disease, however, cannot be established with certainty in this way, as the test continues to evoke a positive reaction for many years after the disease process has healed.

Treatment.—No thoroughly satisfactory therapeutic procedure has as yet been evolved for lymphogranuloma venereum. De Wolf and Van Cleve [31] considered four different types of therapy: chemical, biologic, physical and surgical. In the field of chemical therapy they reported that a 1 per cent solution of antimony and potassium tartrate given intravenously twice a week in increasing doses until from ten to fifteen doses had been administered gave some benefit. Their results with such biologic measures as the injection of foreign protein and vaccine therapy, as well as with autohemotherapy, were doubtful, and their experience with heat and ultraviolet rays was equally unsatisfactory. They found that surgical excision of the glands seemed beneficial and that conservative surgical procedures, varying from dilatation of a stricture to colostomy, were indicated in advanced cases. Frei [32] reported using antimony and gold compounds, which he stated were especially helpful if the infection was in an early stage. Others have used copper, iron and salicylic acid preparations. Chapman and Hayden [33] advised rest in bed, local application of heat, aspiration, surgical incision of the bubo, with drainage if necessary, the use of vaccine, antimony and potassium tartrate, and roentgen rays and, in cases of stricture, dilatation or colostomy.

Sulfanilamide and its related compounds have been found to be of value in combating lymphogranuloma venereum in spite of the fact that in general they have not proved to be useful against virus diseases. MacCallum and Findlay [34] found that white mice inoculated intracerebrally

31. De Wolf, H. F., and Van Cleve, J.: Lymphogranuloma Inguinale, J. A. M. A. **99**:1065 (Sept. 24) 1932.

32. Frei, W.: Venereal Lymphogranuloma, J. A. M. A. **110**:1653 (May 14) 1938.

33. Chapman, E. M., and Hayden, E. P.: New England J. Med. **217**:45, 1937.

34. MacCallum, F. O., and Findlay, G. M.: Lancet **2**:136, 1938.

with the virus of lymphogranuloma venereum and treated with sulfanilamide survived longer and had a lower mortality rate than untreated control mice. The sulfanilamide was totally ineffective, however, when mixed with the infected brain emulsion in vitro before intracerebral inoculation.

Knight and David [35] reported decided improvement following the use of sulfanilamide in a case of lymphogranuloma venereum with anal ulceration and enlargement of the right inguinal gland. In another case, in which an ischiorectal abscess had been incised but was followed by extension into the pelvis, sulfanilamide was given, with prompt healing. The conditions in these cases were of long duration and had made no response to the usual therapeutic measures before the treatment with sulfanilamide was instituted.

Earle [36] treated patients for lymphogranuloma venereum in various stages with sulfapyridine (2-[paraaminobenzenesulfonamide]-pyridine; preparation used, M. & B. 693) and obtained uniformly favorable results. He agreed with the general opinion that the best results are obtained from treatment applied early in the development of the inguinal adenitis but that patients with more advanced lesions may be benefited.

OCULAR INVOLVEMENT IN LYMPHOGRANULOMA VENEREUM

References to ocular signs nad symptoms in relation to lymphogranuloma venereum are encountered infrequently in the literature. Von Haam and D'Aunoy [6] in a report on 461 patients mentioned but 1 in whom conjunctivitis, associated with pain over both eyes and photophobia, occurred. Kornblith [37] reported a flame-shaped hemorrhage in the fundus of 1 patient. Cole [38] noted conjunctivitis in 3 of 37 patients. Liebreich and Gottlieb [39] reported a case of lymphogranuloma venereum with arthritis, a cutaneous eruption and episcleritis. They suggested that the cutaneous eruption was a metastatic manifestation of the disease.

Fundus Changes.—In 1934 Kitagawa [40] examined the eyegrounds of 30 patients with lymphogranuloma venereum and found peripapillary edema and tortuosity of the blood vessels in almost every one. Coutts [4]

35. Knight, A. A., and David, V. C.: Treatment of Venereal Lymphogranuloma with Sulfanilamide, J. A. M. A. **112**:527 (Feb. 11) 1939.

36. Earle, K. V.: Lancet **2**:1265, 1939.

37. Kornblith, B. A.: J. Mt. Sinai Hosp. **3**:24, 1936.

38. Cole, H. N.: Lymphogranuloma Inguinale, Fourth Venereal Disease: Its Relation to Stricture of the Rectum, J. A. M. A. **101**:1069 (Sept. 30) 1933.

39. Liebreich, E., and Gottlieb, F.: Bull. Soc. méd. d. hôp. de Bucharest **14**: 554, 1932.

40. Kitagawa, K.: J. Orient. Med. (Abstr. Sect.) **20**:48, 1934.

examined 10 patients and in 7 found one or all of the following symptoms: edema, dilatation and tortuosity of the veins and an intensely dark red coloration of the circulating blood. Tortuosity of the veins occurred most frequently. In 1 patient with esthiomene and in another with genitoanal symptoms of four years' duration there was the same appearance. Chaigneau [41] reported a series of 87 cases in which changes in the eyegrounds were present in 47.1 per cent, doubtful in 19.5 per cent and absent in 33.3 per cent. Coutts found that the appearance of these ocular manifestations bore no relation to the evolutionary stages of the disease, that the changes might be more extensive in one eye than in the other and that there was no relation between the severity of the fundus changes and any existing visual disturbance.

Parinaud's Oculoglandular Syndrome.—Case reports of Parinaud's oculoglandular syndrome due to infection with the virus of lymphogranuloma venereum have been published. In 1936 Bollack, Basch and Desvignes [42] reported the case of a patient 37 years of age who for six months had had severe follicular conjunctivitis. The preauricular lymph glands were enlarged, and a diagnosis of Parinaud's oculoglandular syndrome was made. No possible cause for the inflammation appeared until the reaction to a Frei test was found to be positive. An emulsion of material taken from the involved gland and injected intracerebrally into a monkey produced the symptoms of lymphogranuloma venereum; an emulsion of the monkey's brain injected into mice intracerebrally resulted in the development of the symptoms of lymphogranuloma venereum in the mice, and an emulsion of the brains of the infected mice gave positive cutaneous reactions in patients known to be infected with the disease.

In 1937 Ichijo [43] reported Parinaud's oculoglandular syndrome in 2 patients who gave positive Frei reactions. Secretion from the eyes of these patients produced positive cutaneous reactions when sterilized and used as an antigen. In the same year Hashimoto, Takenouchi and Ichidyo [44] reported an additional case in which a sterile antigen made from the ocular secretion gave positive cutaneous reactions in 10 patients with lymphogranuloma venereum.

In 1938 Appelmans [3] reported the case of a young physician who was accidentally infected at the University of Louvain, in Belgium. The

41. Chaigneau, A.: Thesis, University of Chile, 1935; cited by Coutts.[4]

42. Bollack, J.; Basch, G., and Desvignes, P.: Bull. Soc. d'opht. de Paris, 1936, p. 409.

43. Ichijo, M.: Acta Soc. ophth. japon. **41**:628, 1937; abstracted, Zentralbl. f. d. ges. Ophth. **39**:541, 1937.

44. Hashimoto, T.; Takenouchi, J., and Ichidyo, M.: Jap. J. Dermat. & Urol. **42**:46, 1937.

right eye became markedly inflamed; there was no ulceration of the conjunctiva and no membrane, but in the inferior cul-de-sac there was some mucofibrinous exudate, in which many pseudodiphtheria bacilli were demonstrated. The injection of antidiphtheritic serum produced no improvement. Material scraped from the conjunctiva was injected into guinea pigs and gave negative results. The preauricular, submaxillary, parotid, sternocleidomastoid and subclavicular glands were swollen.

It was noted that the patient had been working with the virus of lymphogranuloma venereum in the laboratory, and the reaction to a Frei test applied with an antigen prepared from infected mouse brains was positive. Repeated Frei tests gave consistently positive results, while an agglutination test for Brucella tularensis made with the serum gave negative results. It was concluded that the infection was due to the virus of lymphogranuloma venereum.

In 1939 in Java, Ouwejan [45] found 3 patients with Parinaud's oculoglandular syndrome and with positive Frei reactions in whom there was no other apparent cause for the syndrome. There was no response to antisyphilitic therapy, and histologic examination of a piece of conjunctival tissue did not show changes characteristic of syphilis. Tularemia was ruled out on the ground that it has never been known to occur in Java. Ouwejan's attempt to demonstrate the virus of lymphogranuloma venereum was unsuccessful, possibly because the patients came under observation late in the course of the disease.

Curth, Curth and Sanders [46] reported the case of a patient with Parinaud's oculoglandular syndrome whose right eye had been inflamed for five years. The globe appeared to be covered with granulation tissue (fig. 1), and there was extensive symblepharon. The test for tularemia gave negative results, but the Frei reaction was strongly positive and the Wassermann reaction was positive. The patient had been treated surgically for a fistula in ano. Antisyphilitic treatment did not appreciably change the ocular condition, but rapid improvement followed the administration of sulfanilamide.

A portion of the conjunctiva was excised and used for intracerebral inoculation of a monkey. Mild symptoms of lymphogranuloma venereum developed, and histologic examination of the brain showed the characteristic lesions. Washings of the involved conjunctiva were passed through Berkefeld V filters. The filtrate was sterile and was used to inoculate tissue cultures; these in turn were used to inoculate mice intracerebrally, and symptoms of lymphogranuloma venereum developed in

45. Ouwejan, A. J.: Geneesk. tijdschr. v. Nederl.-Indië **79**:1410, 1939.

46. Curth, H. O.; Curth, W., and Sanders, M.: Personal communication to the author.

the mice. Antigens from both tissue culture and infected mouse brain emulsion caused positive Frei reactions in patients known to be infected with the virus of lymphogranuloma venereum. The histologic examination of excised conjunctival tissue showed degenerating stratified squamous epithelium. There was granulation tissue, with polymorphonuclear leukocytes and some eosinophils, surrounding the area of degenerating epithelium. The central portion was made up almost exclusively of round or oval cells with indistinct cell boundaries, eosin-staining cytoplasm and round blue-staining nuclei. The pathologic diagnosis was plasmoma.

Fig. 1.—Parinaud's oculoglandular syndrome caused by infection with the virus of lymphogranuloma venereum.

UVEITIS AND KERATOCONJUNCTIVITIS IN CASES OF SUSPECTED LYMPHOGRANULOMA VENEREUM

Intracutaneous tests according to the technic of Frei were performed on a series of 30 patients with uveitis or keratoconjunctivitis, some of whom were selected because of suspected lymphogranuloma venereum. Four of these gave positive reactions when first tested. Subsequent tests in 2 of the 4 gave negative results, and in 1 repeated positive reactions were obtained. In each of the 4 patients pathologic conditions other than the evidence of lymphogranuloma venereum were found which could have been etiologic factors in the ocular disease. The case histories follow.

REPORT OF CASES

CASE 1.—A. W., a Negress aged 47, came to the ophthalmologic department of the Vanderbilt Clinic on July 17, 1939. She complained of pain and irritation of both eyes of two weeks' duration. The vision of the right eye was 20/20—2 and of the left 20/40. The right pupil was round, while the left was slightly oval; both pupils reacted to light and in accommodation, and the consensual reflex was present on both sides. There was conjunctival and ciliary injection of both eyes, more distinct on the left side. The intraocular tension was 16 mm. of mercury in the right eye and 35 mm. in the left with the new Schiötz tonometer. Numerous cells were visible in both anterior chambers, and there were deposits on the posterior surface of each cornea. The interiors of the eyes showed no abnormality. The visual fields were normal. A diagnosis of uveitis and secondary glaucoma of both eyes was made. Further clinical investigations revealed that the Frei reaction was positive on one occasion and negative on another; the Wassermann reaction of the blood was negative on two occasions; the Mantoux reaction was positive; the intradermal test for brucellosis gave negative results, and the gynecologic, dental, aural, nasal, pharyngeal and general physical examinations revealed no focus of infection, although the roentgen ray examination was reported as showing the right frontal sinus to be slightly cloudy.

The pupils were dilated with atropine, and hot compresses were applied. The intraocular tension of the left eye rose to 49 mm. of mercury, and paracentesis was performed on July 19. The wound was reopened daily for twelve days, and the tension returned to normal, where it has remained. On July 28 the intraocular pressure of the right eye became elevated to 66 mm. of mercury, and paracentesis was performed on this eye. The surgical wound was reopened daily for eleven days, at the end of which time the tension fell to within normal range, where it has remained.

Intravenous typhoid vaccine was used to produce a temperature of from 102 to 104 F. on six occasions during the first two weeks. On August 8 proctoscopic examination showed inflammation of the rectal mucosa compatible with lymphogranuloma venereum. Azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) was prescribed, and the ocular and rectal inflammatory signs subsided.

The subsidence of the ocular and rectal inflammation with azosulfamide therapy suggests that the virus of lymphogranuloma venereum may have been the cause.

CASE 2.—P. T., a Negro porter aged 48, came to the department of proctology of Vanderbilt Clinic on Sept. 26, 1938. A diagnosis of fistula of the anus was made, and a Frei test was done, the result of which was reported positive. The Wassermann reaction of the blood was also positive.

On November 7 a perirectal abscess was excised and antisyphilitic therapy was instituted.

The patient came to the ophthalmologic department of the Vanderbilt Clinic on Feb. 6, 1939. He complained of irritation and watering of the left eye. This had been present for several weeks. The corrected vision of the right eye was 20/20 and of the left 20/20. The right eye was normal. There was conjunctival and ciliary injection of the left eye, which showed peripheral infiltration and vascularization of the corneal stroma. The left cornea showed numerous small areas which stained with fluorescein. There were no cells in the anterior chamber or deposits on the posterior surface of the cornea of either eye. The iris and pupillary reactions were normal. Cultures made from the conjunctiva of the left eye showed a heavy growth of Staphylococcus aureus. The preauricular glands

were not palpable. A diagnosis of keratitis and conjunctivitis of the left eye was made. Repeated Wassermann tests of the blood gave strongly positive reactions; the reaction to a tuberculin test was positive, while the result of an intradermal test for brucellosis was negative. Aural, nasal, pharyngeal, dental and general physical examinations revealed no focus of infection.

The left eye was treated by the instillation of atropine sulfate, 1 per cent solution, and the application of silver nitrate, 0.25 per cent solution, to the palpebral conjunctivas. The injection of the eye became more intense; wrinkles of Descemet's membrane appeared, and cells were to be seen in the anterior chamber. Staphylococcus toxoid therapy was instituted.

On February 21 the anterior chamber of the left eye was tapped, and the aqueous which was removed was used for intracerebral injection into white mice. No symptoms developed in these animals.

There was gradual improvement in the condition of the eye during the weeks following the use of staphylococcus toxoid therapy; the injection subsided, and the cornea cleared.

In this case of keratoconjunctivitis in a patient with syphilis and lymphogranuloma venereum, the local infection with Staph. aureus was probably responsible for the pathologic changes in the eye.

Case 3.—A. W., a white woman aged 23, a school teacher, came to the Vanderbilt Clinic on June 26, 1936. A diagnosis of rectovaginal fistula was made. An operation for plastic repair of the fistula was performed and was followed by normal convalescence.

The patient returned to the Vanderbilt Clinic on Aug. 8, 1939, and came to the ophthalmologic department, complaining of irritation and poor vision of the left eye of a week's duration. The vision of the right eye was 20/30 + and of the left 8/200. The right eye was normal, while the left eye showed ciliary injection. There were many cells in the anterior chamber and deposits on the posterior surface of the cornea of the left eye. The interior of this eye showed many stringy vitreous opacities which obscured the fundus; however, a vague whitish area near the disk could be seen. The intraocular tension of the right eye was 16 mm. of mercury and that of the left 19 mm. with the new Schiötz tonometer. A diagnosis of uveitis and choroiditis of the left eye was made. The Frei test gave a positive reaction on one occasion, and when repeated, gave a negative result. The Wassermann reaction of the blood was negative. A tuberculin test with a dilution of 1:1,000,000 gave a negative, and one with a dilution of 1:100,000 a positive, result. An intradermal test for brucellosis gave a negative result. The aural, pharyngeal and general physical examinations revealed no evidence of a focus of infection. The roentgen ray examination revealed a cloudy left antrum and evidence of dental infection.

The pupil was dilated with atropine sulfate; hot compresses were applied, and typhoid vaccine was administered intravenously, producing a temperature elevation of 105 and 104.6 F. The left antrum was irrigated and thick mucopurulent material obtained. Dental infection was eliminated. There was a gradual subsidence of the activity of the left eye over a period of months.

Tuberculosis or dental or sinus infection may have been the cause of the ocular inflammation in this patient. The positive Frei reaction suggests lymphogranuloma venereum as another possibility.

Case 4.—M. P., a Negress aged 30, came to the department of proctology of Vanderbilt Clinic on Feb. 28, 1939. A diagnosis of stricture and ulceration of

the rectum was made, and lymphogranuloma venereum was suggested as the cause. It was noted that the eyes were irritated, and the patient was referred to the ophthalmologic department. It was found that the Frei reaction had been positive on Nov. 28, 1938, when the patient was tested by the Board of Health of the City of New York. The patient was given azosulfamide, and there was great improvement in the condition of the eyes, as well as in the rectal stricture and ulceration.

On March 2, 1939 she came to the ophthalmologic department complaining of redness and swelling of the lids and irritation of both eyes. The eyes had been becoming progressively worse for seven months. The vision of the right eye was 20/70 and of the left 20/100 — 1. The lids of both eyes were red and swollen. There was distinct conjunctival and ciliary injection. The corneal stroma of both eyes was vascularized and infiltrated. Numerous small superficial areas of both corneas stained with fluorescein. No cells were to be seen in the anterior chambers, and no deposits were visible on the posterior surface of the corneas. The pupils, irises and interiors of both eyes were normal. The preauricular glands were not palpable. A diagnosis of keratitis and conjunctivitis of both eyes was made. Cultures made from the conjunctivas showed Staph. aureus. The Frei test was repeated, and on three of four occasions the result was positive. The Wassermann reaction of the blood was weakly positive in one of two tests. The reaction to a tuberculin test was doubtful on one occasion and negative on another. The intradermal test for brucellosis gave a negative result. The dental, aural, nasal, pharyngeal and general physical examinations revealed no focus of infection.

On March 27 the anterior chamber of the left eye was tapped, and the aqueous which was removed was used for intracerebral inoculation of white mice. This was not followed by the development of any symptoms of lymphogranuloma venereum in any of the inoculated animals.

Atropine sulfate, 1 per cent solution, was instilled into both eyes, and silver nitrate, 0.25 per cent solution, was applied daily to the palpebral conjunctivas, with little change in the condition. Antisyphilitic treatment was continued. Treatment with azosulfamide caused great improvement of both rectal and ocular symptoms.

This patient had both lymphogranuloma venereum and syphilis, as well as a staphylococcic infection, which can cause ocular inflammation. The coincident improvement of the ocular and rectal inflammations after treatment with azosulfamide suggests a common cause for both conditions and that lymphogranuloma venereum may have been the etiologic factor.

INOCULATION OF ANIMAL EYES WITH THE VIRUS OF LYMPHOGRANULOMA VENEREUM

In 1924 Hansmann [47] inoculated material from a bubo of a patient with lymphogranuloma venereum into a rabbit's eye. This was followed by panophthalmitis, which destroyed the eye. The same material was inoculated subcutaneously and intraperitoneally into guinea pigs, rabbits, rats and mice without causing any symptoms. In the same year Gamna [23] inoculated the anterior chambers of rabbits' eyes with material from an enlarged gland in a patient with lymphogranuloma venereum. The eyes

47. Hansmann, G.: Surg., Gynec. & Obst. **39**:72, 1924.

remained normal. In 1932 Findlay [48] noted that after the intracerebral inoculation of monkeys with infected material, the pupils were dilated, sometimes unequally, and there was incoordination of the extraocular muscles of the eye. Levaditi, Schoen and Reinié [49] inoculated a chimpanzee by subconjunctival injection of material containing the virus of lymphogranuloma venereum; a marked reaction similar to Parinaud's oculoglandular syndrome resulted.

Miyagawa, Mitamura, Yaoi, Ishii and Okanishi [50] inoculated the anterior chamber of rabbits with infective material and produced hyperemia of the eye with turbidity of the cornea and iritis. These findings were not constant, and no granulocorpuscles were found in smears taken from Descemet's membrane or from the iris. When Satani and Sano [51] repeated these tests in rabbits and guinea pigs, keratitis and conjunctivitis with iritis were produced in both animals. The aqueous removed from inflamed eyes transmitted the infection to mice by intracerebral inoculation, and these mouse brains yielded antigens which produced positive Frei reactions. Granulocorpuscles were demonstrated in smears made from Descemet's membrane and from infected mouse brains.

Von Haam and Hartwell [52] noted unilateral or bilateral conjunctivitis following intracerebral inoculation with the virus of lymphogranuloma venereum in white mice, monkeys, ferrets, cats, sheep and calves. Findlay [53] observed corneal opacity and iridocyclitis followed by atrophy of the eyeball after inoculation of the anterior chamber of rabbits with infected inguinal gland material. Cottini [54] inoculated mice intracerebrally with material from a bubo, and purulent conjunctivitis developed. The eyes were emulsified, and when the material was inoculated intracerebrally into other mice, symptoms of lymphogranuloma venereum were produced. In smears from these infected mouse brains, granulocorpuscles could be demonstrated.

AN EXPERIMENTAL STUDY

The material used for the inoculation of animals in this series of experiments was virus obtained from the laboratory of Strauss and Howard, Department of Internal Medicine, Yale University, New Haven, Conn. It was isolated from human glandular material in August 1938. During the course of this study the virus has been maintained

48. Findlay, G. M.: Lancet **2**:11, 1932.

49. Levaditi, C.; Schoen, R., and Reinié, L.: Compt. rend. Acad. d. sc. **203**: 828, 1936.

50. Miyagawa, Y.; Mitamura, T.; Yaoi, H.; Ishii, N., and Okanishi, J.: Jap. J. Exper. Med. **14**:197, 1936.

51. Satani, Y., and Sano, J.: Jap. J. Exper. Med. **14**:523, 1936.

52. von Haam, E., and Hartwell, R.: J. Trop. Med. **39**:190, 1936.

53. Findlay, G. M.: Tr. Roy. Soc. Trop. Med. & Hyg. **31**:6, 1938.

54. Cottini, G. B.: Riforma med. **54**:901, 1938.

in tissue cultures consisting of embryonic guinea pig brain in serum ultrafiltrate and by intracerebral mouse inoculation in the laboratories of Columbia University College of Physicians and Surgeons by Dr. Murray Sanders.

After intracerebral inoculation of 0.03 cc. of infected tissue culture or emulsified infected mouse brain, the majority of animals within a few days showed symptoms suggestive of infection due to lymphogranuloma venereum, i. e., ruffled coat, humped back, emaciation, ataxia, paresis and paralysis of the hindlegs. Emulsions of the brains of these animals were bacteriologically sterile in aerobic and anaerobic cultures and caused cutaneous reactions similar to positive Frei reactions in patients known to have lymphogranuloma venereum.

Inoculation of Nineteen Guinea Pig Eyes.—Procedure: A suspension of mouse brain infected with the virus of lymphogranuloma venereum was injected into the anterior chamber of one eye of each of 19 guinea pigs. The margins of the lids and structures about the eyes were first cleansed with 3.5 per cent solution of iodine, and the conjunctival sacs were flushed with 25 per cent solution of mild silver protein. Ether anesthesia was used. Fixation was obtained by grasping the conjunctiva and episcleral tissue near the limbus with forceps. A 27 gage hypodermic needle attached to a tuberculin syringe containing infected mouse brain suspension was passed obliquely through the cornea into the anterior chamber. About 0.02 cc. of aqueous was withdrawn into the syringe and then reinjected. This was repeated several times until it was seen that cloudy material had entered the eye, indicating that the brain suspension had mixed with the withdrawn aqueous. In order to avoid elevating the intraocular tension, care was exercised that the volume of material introduced into the eye was no more than that withdrawn. After the needle was removed, the puncture closed with little if any loss of the content of the anterior chamber. The occasional bubbles observed in the anterior chamber disappeared in from twenty-four to forty-eight hours.

Results: In 13 of the 19 inoculated eyes a conjunctival injection with chemosis of the conjunctiva, associated with infiltration and peripheral vascularization of the cornea, appeared in from twenty-four to forty-eight hours. This increased in intensity until a band of vascularized cornea 2 mm. in width surrounded the densely infiltrated central zone, through which the deeper structures of the eye could not be seen. The process reached maximum intensity in from seven to ten days and then slowly subsided, the eye in no instance returning entirely to normal during the ten week period of observation (fig. 2). The intraocular tension seemed to be low normal in all of these 13 eyes but 1. In this eye ectasia of the cornea developed.

In the 6 remaining eyes, at the sites of fixation there was slight injection, which appeared immediately and gradually subsided in from

three to five days. In the corneas, at the sites of puncture there was slight infiltration, which was also gradually absorbed. Two of the suspensions used in the inoculation of this group failed to induce infection on further passage in mice, which would seem to indicate that the virus either was not present or had been destroyed or inactivated.

The results of the inoculations were in all instances definitely positive or negative with the exception of the eye in which ectasia of the cornea developed. After the operation several eyes in both groups showed slight

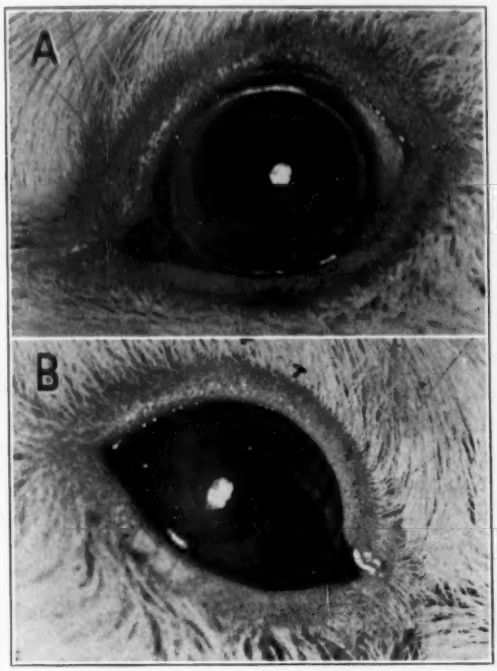


Fig. 2.—*A*, normal guinea pig eye. *B*, guinea pig eye seven days after the introduction of material containing the virus of lymphogranuloma venereum into the anterior chamber.

linear lenticular opacity, which did not tend to progress during the period of observation.

Aqueous removed from the anterior chamber of 1 eye during the acute stage of the infection was bacteria free.

A suspension of normal mouse brain prepared and inoculated in the same manner produced only negligible inflammation in 5 control eyes.

Inoculation of Four Rabbit Eyes.—The same procedure was carried out in 4 rabbit eyes with the exception that a larger amount of aqueous, approximately 0.15 cc., was withdrawn and a correspondingly larger

amount of infected brain emulsion introduced into the eyes. In only 1 eye did inflammation follow, and this was of much less intensity and shorter duration than the reaction in the eyes of the guinea pigs. This observation confirms that of other investigators who have found the rabbit an unsatisfactory animal for experimental work with lymphogranuloma venereum.

Pathologic Observations.—The right eye of guinea pig 5, which was acutely inflamed after inoculation with infected mouse brain emulsion, was enucleated seven days after inoculation, and the similarly infected right eye of guinea pig 7 was enucleated on the ninth day after inoculation. These eyes were fixed in Bouin's fluid, sectioned and stained with hematoxylin and eosin.

Guinea Pig 5: The corneal epithelium was intact. There was no leukocytic infiltration of the epithelium. The central two thirds of the stroma showed decided separation of the lamellae, the spaces being filled in by a more or less granular pink-staining albuminous fluid, in which there were numerous polymorphonuclear leukocytes. These inflammatory cells were also present between the unseparated lamellae. Extending in from each limbus were many new-formed blood vessels. In the periphery of the cornea there was a large amount of infiltration consisting of polymorphonuclear and lymphocytic leukocytes. There was a break in Descemet's membrane at one point, the cut edges being retracted.

The anterior chamber was deep. Both angles were filled with exudate and fibrin. A granular pink-staining fluid filled the chamber. The endothelium was largely degenerated, the cells were swollen, the cytoplasm was practically absent and only the nuclei stained in most of the cells. Groups of polymorphonuclear leukocytes and monocytic cells lay on the endothelium. The ciliary body on each side and the entire iris stroma were infiltrated with inflammatory leukocytes. The ciliary body showed much more involvement than the iris stroma.

The lens was in place and showed no gross pathologic change. The anterior portion of the choroid showed some leukocytic infiltration, while the posterior portion was essentially normal. The retina proper was detached, as a result of fixation, but showed no pathologic change. In the vitreous were a few scattered cells, which appeared to be large phagocytic mononuclear cells. The small segment of optic nerve, which was all that appeared in the sections, showed no pathologic changes (fig. 3).

Guinea Pig 7: This eye showed the same type of corneal, iridic and ciliary body involvement as the eye of guinea pig 5. One limb of the iris was adherent to the lens capsule at the pupillary border, and a fibrinous membrane extended along the anterior lens capsule. The optic

nerve head was shown in several of these sections, but there was no evidence of neuritis (figs. 4 and 5).

The pathologic diagnosis in both cases was keratitis and acute iridocyclitis.

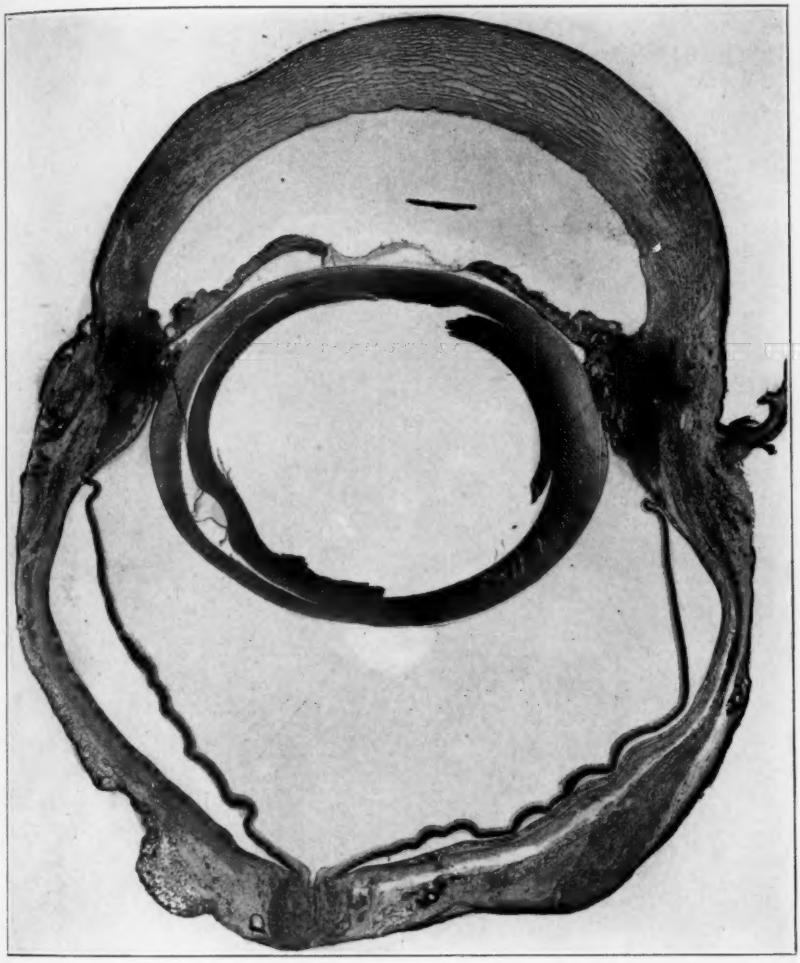


Fig. 3.—Eye of guinea pig 5 (× 10). Keratitis and iridocyclitis seven days after the introduction into the anterior chamber of material containing the virus of lymphogranuloma venereum. The lamellae in the central portion of the cornea are separated. The cornea, iris and ciliary body are infiltrated with leukocytes. There is a fibrinous membrane extending along the anterior lens capsule.

Specificity of the Infection.—In an effort to establish the specificity of the infection produced by these inoculations, the following experiments were undertaken:

1. The Transfer of the Infection from the Eye of One Guinea Pig to the Eye of Another by the Transfer of Aqueous: The aqueous was withdrawn from guinea pig eyes in the acute stage of the inflammation and inoculated into 7 normal guinea pig eyes. In no case did inflamma-

Fig. 4.—Region at the angle of the anterior chamber of an eye of guinea pig 7 (× 30). Keratitis and iridocyclitis with adhesion of the iris to the lens at the pupillary border. The scar in the cornea produced at the time of inoculation with the virus of lymphogranuloma venereum nine days before is shown. There is leukocytic infiltration into the cornea, with blood vessels in the corneal stroma near the limbus. The angle is filled with exudate and fibrin. The iris stroma and ciliary body are infiltrated with leukocytes.

tion result more intense than that which normally would follow manipulation of the eye and puncture of the cornea.

2. The Transfer of the Infection from the Eye of a Guinea Pig or Rabbit to Mice by the Intracerebral Injection of Aqueous Removed from an Infected Eye: Aqueous from rabbit 4, in which an inflammation developed after inoculation of the anterior chamber with infected mouse

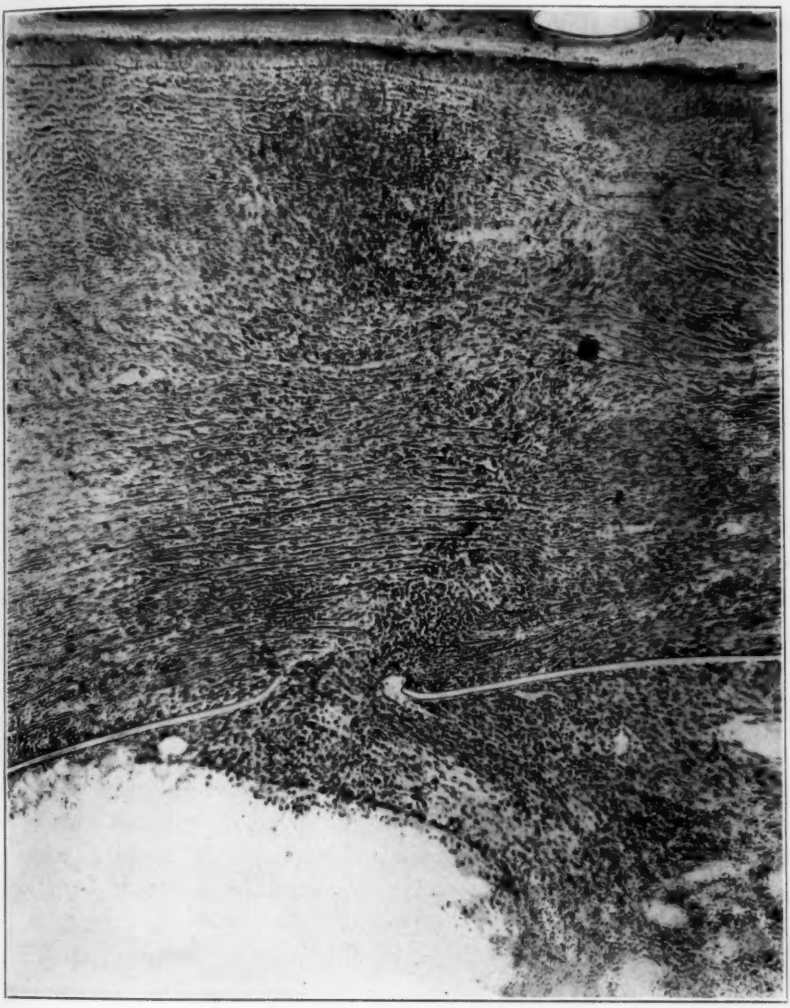


Fig. 5.—The cornea and adjacent angle of the eye of guinea pig 7 (× 95). The injury of the cornea produced by inoculation with the virus of lymphogranuloma venereum nine days before is shown. The cut edges of Descemet's membrane are retracted. The cornea is infiltrated with leukocytes, and there are blood vessels in the stroma. Fibrin and exudate fill the angle.

brain emulsion, was removed seven days after the operation and inoculated intracerebrally into 4 mice; in all 4 symptoms of lympho-

granuloma venereum developed within five days. An emulsion was prepared from the brain of 1 of these and inoculated intracerebrally into 4 more mice, in all of which similar symptoms developed. The brains of 2 of these were used to prepare another emulsion, which was bacteriologically negative and was used to inoculate 12 additional mice intracerebrally. In all these mice the symptoms of lymphogranuloma venereum developed, and an emulsion prepared from the brain of 1 produced an acute inflammation in 1 of 3 guinea pig eyes inoculated in the anterior chamber.

Aqueous removed from the acutely inflamed eye of guinea pig 11 produced symptoms in 2 mice inoculated intracerebrally, and aqueous from the inflamed eye of guinea pig 14 produced symptoms in 3 mice inoculated intracerebrally. Emulsions of the mouse brains infected from both these guinea pigs did not cause inflammation when inoculated into the anterior chambers of normal guinea pig eyes.

Normal guinea pig aqueous when injected intracerebrally into mice produced no symptoms.

3. Cultivation of the Virus in a Tissue Culture Inoculated by the Addition of Aqueous from an Infected Eye: Aqueous from the anterior chamber of the inflamed eye of guinea pig 11 was added to a tissue culture; after cultivation at room temperature for twelve days an antigen prepared from this culture was used in a Frei test on a patient known to have lymphogranuloma venereum; the reaction was positive.

4. Demonstration of Dermal Reactions to the Antigen of the Virus in Infected Guinea Pigs: Antigen from the brains of mice which had been inoculated with the virus and in which symptoms characteristic of lymphogranuloma venereum had developed, and control material from normal mouse brain were sterilized by fractional heating according to the technic followed in the preparation of material for the Frei test. Intradermal injection of sterile antigen and control material was performed on 3 normal and 9 infected guinea pigs. Positive cutaneous reactions were obtained in 4 of the infected animals, doubtful positive reactions in 2 and negative reactions in 3. The 3 control injections gave negative results.

5. Demonstration of Evidence of Infection in Scrapings from the Posterior Surface of the Cornea and in Smears from Iris Tissue: The corneas of 7 guinea pig eyes which were acutely inflamed after inoculation with infected mouse brain emulsion were excised. Smears prepared by scraping the iris and the posterior surface of the cornea were stained according to the Giemsa method. Structures of varying size resembling the elementary and initial bodies of trachoma were identified (fig. 6).

Comment: Transfer of the infection from 1 guinea pig eye to another in experiment 1 may have failed because too few of the elements of

infection were present in the aqueous. The positive results of intracerebral injection of aqueous in mice may have been effected because brain tissue is a better environment for the development of the virus.

The cutaneous reactions in the guinea pigs were inconsistent. These animals are generally considered to be unsatisfactory for this type of test, but positive reactions were obtained in a sufficient number of cases to suggest the specific nature of the infection.

The demonstration of inclusion bodies in the smears made from the surfaces of the iris and cornea of the infected guinea pig eyes suggests

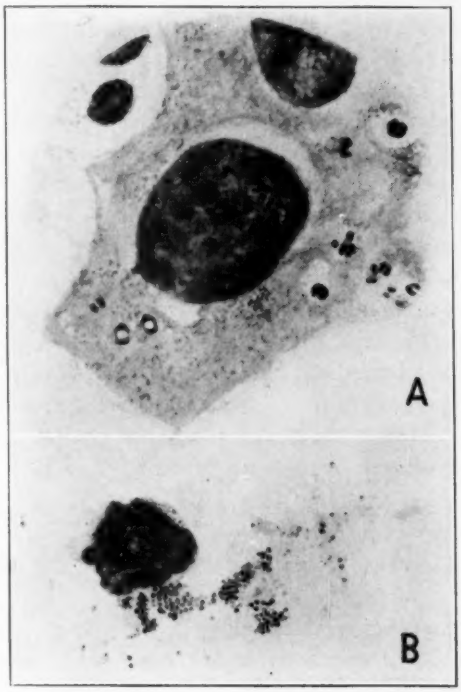


Fig. 6.—*A*, scrapings from the posterior surface of the cornea and the iris of a guinea pig eye at the onset of acute inflammation following inoculation with the virus of lymphogranuloma venereum. Ring forms resemble the initial bodies of trachoma. (Giemsa stain; drawn from magnification of 1,350.) *B*, similar scrapings, in which granules resemble the elementary bodies of trachoma. (Giemsa stain; drawn from magnification of 1,350).

that the virus was developing in the structures adjacent to the anterior chamber. No inclusions could be demonstrated in similar smears from normal guinea pig eyes or in smears made from infected mouse brains.

SUMMARY

Lymphogranuloma venereum is a widespread venereal disease, which is probably more common than is generally realized. It is caused by a

virus. The insignificant inoculatory lesion is followed by involvement of the regional lymph glands, and the disease may progress to esthiomene, inflammatory stricture of the rectum or other lesions of the anus, perineum or rectum. Associated constitutional symptoms and occasional remote lesions indicate that the infection is sometimes generalized. Extragenital infections have occurred.

The virus is filtrable but of large particle size, measuring between 0.125 and 0.175 microns. It has been grown in tissue culture, and intracellular and extracellular granulocorpuscles, believed to be virus particles, have been demonstrated.

That antibodies are developed is indicated by the result of a Frei test (a specific cutaneous reaction of patients with the disease to sterilized exudate from an active lesion).

Monkeys, white mice and ferrets are the most susceptible animals, and experimental infection is best induced by intracerebral inoculation, which produces meningoencephalitis, frequently fatal.

The pathologic changes, which are not entirely characteristic, consist of ulceration or infiltration at the site of the inoculation, enlargement of the regional glands, which may break down and drain, progress of the process by endolymphangitis and perilymphangitis and a tendency to spread to adjacent tissues. Secondary infection may occur and may be a factor in the development of the characteristic lesions of the third stage.

The disease may be confused with chancroid, syphilis, tuberculosis, malignant tumor, Hodgkin's disease, bubonic plague, tularemia, granuloma inguinale, dysentery or ulcerative colitis. The Frei test is a reliable indicator of infection at some time with the virus of lymphogranuloma venereum (98.1 per cent, according to one report) but fails to indicate activity of the disease, as it usually continues to give positive reactions years after the subsidence of symptoms.

There is no thoroughly satisfactory treatment for lymphogranuloma venereum. The use of antimony, gold, copper and iron compounds; of salicylic acid and potassium tartrate; of foreign protein, heat and ultraviolet radiation; of surgical incision and excision of glands, and of dilatation or colostomy for stricture have been reported. Sulfanilamide and its related compounds appear to be of considerable value.

Cases of lymphogranuloma venereum showing conjunctivitis, retinal hemorrhages, episcleritis and peripapillary edema, as well as dilatation, tortuosity or dark coloration of the retinal vessels, have been reported.

Nine cases of Parinaud's oculoglandular syndrome in patients infected with the virus of lymphogranuloma venereum have been reported. In 4 of these the conjunctival secretion or excised conjunctival tissue has been shown to contain the virus.

A series of 30 patients with keratoconjunctivitis and uveitis were subjected to the Frei test. Of these, 4 reacted positively and were

found to have rectal symptoms consistent with lymphogranuloma venereum. Other pathologic conditions in all 4 cases could have accounted for the ocular symptoms, but lymphogranuloma venereum was an etiologic possibility in 3.

Successful inoculations of animal eyes with the virus of lymphogranuloma venereum and successful transfer from eye to eye by means of infected aqueous have been reported. Infected aqueous has also been known to produce characteristic meningoencephalitis in white mice, and antigens from these infected brains have given positive Frei reactions. Granulocorpuscles have been reported in scrapings from the posterior surface of the cornea of experimentally infected eyes.

An experimental study was undertaken in an effort to confirm the foregoing findings: 1. Keratitis and uveitis were produced in the eyes of 13 of 19 guinea pigs by injecting infected mouse brain emulsion into the anterior chamber. 2. The infection could not be introduced into other guinea pig eyes by transfer of aqueous. 3. Some of the same aqueous inoculated intracerebrally produced the symptoms of lymphogranuloma venereum in white mice. 4. Infected aqueous was introduced into a tissue culture, and an antigen from this culture produced a positive Frei reaction. 5. Tests for cutaneous sensitivity in 9 infected guinea pigs yielded four positive, two doubtful and three negative results. 6. Smears from the iris and posterior surface of the cornea of infected guinea pig eyes, when stained according to the Giemsa method, showed structures of varying size resembling the elementary and initial bodies of trachoma.

CONCLUSIONS

The virus of lymphogranuloma venereum is one of the causes of the oculoglandular syndrome of Parinaud and may be a cause of other ocular diseases, particularly of inflammations of the uveal tract. It should be considered as a possible causal factor in ocular infections of unknown etiology.

Dr. M. Sanders, of the department of bacteriology of the College of Physicians and Surgeons, made available material containing the virus of lymphogranuloma venereum used in this study.

DIPLOBACILLUS OF PETIT IN CORNEAL ULCERATION

REPORT OF THREE CASES

ALFRED J. ELLIOT, M.D.

WEBB P. CHAMBERLAIN JR., M.D.

AND

ISADORE GIVNER, M.D.

NEW YORK

The presence of a gram-negative diplobacillus in corneal ulceration having the characteristics described by Petit [1] in 1899 has been reported frequently in the European literature. In America, however, either the occurrence of this organism is very infrequent or its bacteriologic differentiation from the diplobacillus of Morax-Axenfeld has not been made or cases have not been reported. This report is presented because 3 cases were observed within a short time, and in 2 of the cases the corneas were obtained for histologic examination.

REVIEW OF THE LITERATURE

Studies of diplobacillary keratitis have been made by several observers,[2] but differentiation was not made between the diplobacillus of Morax-Axenfeld and that of Petit. It has been pointed out by Gifford [3] that the differentiation between the diplobacillus of Petit and that

From the Department of Research, New York Eye and Ear Infirmary.

1. Petit, P.: Sur une forme particulière d'infection cornéenne à type serpigneux, Ann. d'ocul. **140**:166, 1899.

2. Smith, D.: One Hundred Cases of Eye Disease with Bacteriological Examination, Yale M. J. **10**:393, 1904. Erdmann, P.: Ein Beitrag zur Kenntnis der Diplobazillengeschwüre der Kornea nebst Untersuchungen über die Widerstandsfähigkeit der Diplobazillen gegen Austrocknung in Sekretin, Klin. Monatsbl. f. Augenh. **43**:561, 1905. Pusey, B.: The Diplobacillus of Morax-Axenfeld, J. A. M. A. **47**:255 (July 28) 1906. Weeks, J. E.: The Pathogenic Bacteria of the Eyeball, ibid. **47**:324 (Aug. 4) 1906. Duane, A., and Hastings, T. W.: Bacterial Types of Acute Conjunctivitis, New York M. J. **83**:1122, 1906. McKee, H.: Ulceration of the Cornea from the Diplobacillus of Morax-Axenfeld, Ophth. Rec. **16**:183, 1907. Löwenstein, A.: Ueber histologische Befunde beim Diplobazillengeschwüre der Hornhaut, Klin. Monatsbl. f. Augenh. **16**:286, 1913. Gifford, S.: Ulcer of Cornea, Am. J. Ophth. **4**:460, 1921.

3. Gifford, H.: Diplobacillus of Morax and Axenfeld, Ophth. Rec. **14**:511, 1905.

of Morax-Axenfeld could be made only by study of cultures. However, Rosenhauch,[4] Oreste,[5] Zade[6] and Wirtz[7] described cases of corneal ulceration in which the diplobacillus of Petit was identified.

The Petit and the Morax-Axenfeld diplobacilli were regarded as identical by Tooke[8] and Paul.[9] Macnab[10] and Axenfeld[10a] stated that after a time the Petit diplobacillus loses its property of liquefying gelatin and that the Morax-Axenfeld diplobacillus does not grow on serum-free mediums. According to Chaine,[11] the two organisms are distinct biologically and culturally. He maintained that the precipitation, agglutination and fixation of complement reactions make possible their differentiation.

In 1917 Scarlett[12] described a new diplobacillus which grew on blood serum and gelatin but did not liquefy them. He recorded 1 case of corneal ulceration in which the diplobacillus of Petit was found, but he has not encountered the organism since that time.[13] More recently Gifford[14] identified gram-negative diplobacilli in 2 cases, in 1 of which the gelatin was liquefied while in the other liquefaction was doubtful. In 1936 Soudakoff[15] reported 3 cases of corneal ulceration in which the condition was produced by the diplobacillus of Petit.

CLINICAL PICTURE

The lesion starts as a central gray infiltration, which slowly develops into an ulcer with a gray membranous base. Two infiltrated zones are often apparent, one around the ulcer and a second in the deeper part of

4. Rosenhauch, E.: Ueber hypopyon Keratitis mit seltenen bakteriologischen Befunden, Klin. Monatsbl. f. Augenh. **47**:257, 1909.

5. Oreste, A.: Les infections cornéennes en général et l'ulcère à diplobacille de Petit en particulier, Ann. d'ocul. **142**:266, 1909.

6. Zade, M.: Beitrag zur Kenntnis des Diplobazillengeschwüre der Hornhaut, Klin. Monatsbl. f. Augenh. **46**:153, 1908.

7. Wirtz, R.: Die Ionentherapie in der Augenheilkunde, Klin. Monatsbl. f. Augenh. **46**:543, 1908.

8. Tooke, F. T.: Morax-Axenfeld Conjunctivitis, Ophth. Rec. **15**:194, 1906.

9. Paul, L.: Ueber Hornhautulcerationen durch Diplobazillen, Klin. Monatsbl. f. Augenh. **43**:154, 1905.

10. Macnab, A.: The Bacteriology of Ulceration of the Cornea, Ophthalmoscope **8**:629, 1910.

10a. Axenfeld, T.: The Bacteriology of the Eye, translated by A. Macnab, London, Baillière, Tindall & Cox, 1908.

11. Chaine, R.: Le diplobacille de Morax et le diplobacille liquéfiant de Petit (étude comparée), Ann. d'ocul. **152**:330, 1914.

12. Scarlett, H.: Diplobacilli in Corneal Ulcers, Arch. Ophth. **46**:219, 1917.

13. Scarlett, H.: Personal communication to the authors, July 27, 1939.

14. Gifford, S.: Personal communication to the authors, July 17, 1939.

15. Soudakoff, P. S.: Keratitis Ulcerosa and Non-Ulcerosa Produced by Diplobacillus Petit, Chinese M. J. **50**:1415, 1936.

the stroma, between which there is clear cornea. The ulcer has a tendency to spread deeply, and hypopyon may occur. The border is usually not undermined.

Associated conjunctivitis is not generally present, and very little, if any, chemosis of the conjunctiva is seen. The lacrimal sac is usually free of infection.

As a rule, there is only moderate discomfort in the eye, although severe pain may occur. Photophobia is not intense, and general reaction and fever are rare.

The bacteria can be found in smears of material taken from the base of the ulcer. The organisms are not obtained frequently in the conjunctival sac.

A history of trauma at the incipiency of the condition is often noted. Almost all the patients have been adults, and the condition is usually monocular.

REPORT OF CASES

The cases are from the service of the late Dr. Webb W. Weeks at the New York Eye and Ear Infirmary.

CASE 1.—M. G., aged 54, white, appeared at the hospital on June 15, 1939, with the complaint that his left eye had been irritated for one week.

Examination revealed slight conjunctival congestion with no secretion. There was an ulceration in the center of the cornea. The upper border seemed to be advancing, yet there was no cicatrization of the lower border. The infiltration was deep, penetrating into Descemet's membrane, which was wrinkled. The iris was congested, but no cells were seen in the anterior chamber. The tension was normal.

The ulcer was curetted, 1 per cent atropine sulfate was instilled and the eye was covered with a patch. Bacteriologic examination of the material obtained with the curet showed that the organism was the diplobacillus of Petit.

Unfortunately, the patient did not return and could not be located for further observation.

CASE 2.—O. I., aged 66, white, was seen on Jan. 9, 1940, complaining of moderate pain and redness of the right eye, with discharge, for one week. There was a history of long-standing secondary glaucoma with complete loss of vision.

Examination revealed a small amount of mucopurulent material in the conjunctival sac. The margins of the eyelids were red and swollen. The cornea showed superficial necrosis extending in a vertical direction nasally and temporally, with deep infiltration of the cornea between the lower extremities of the necrotic area. Only slight staining was present with fluorescein over the deeply infiltrated area (fig. 1). Circumcorneal injection was present. No hypopyon was seen, and the lacrimal sac was free of pus. The tension of the eye was elevated.

Bacteriologic examination of the material taken from the base of the ulcer revealed the diplobacillus of Petit.

Treatment consisted of the instillation of drops of 1 per cent zinc sulfate three times a day into the eye and the application of 0.5 per cent zinc sulfate ointment at night.

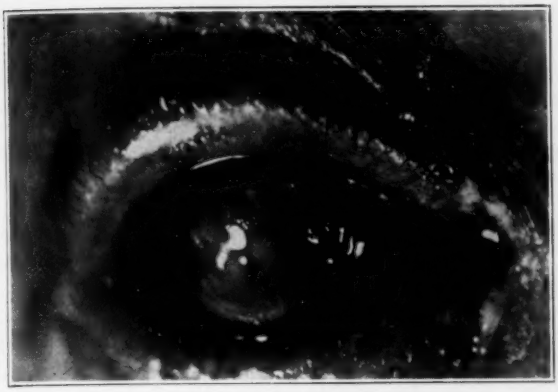


Fig. 1.—Ulcer produced by the diplobacillus of Petit, showing the deep infiltration in the cornea.

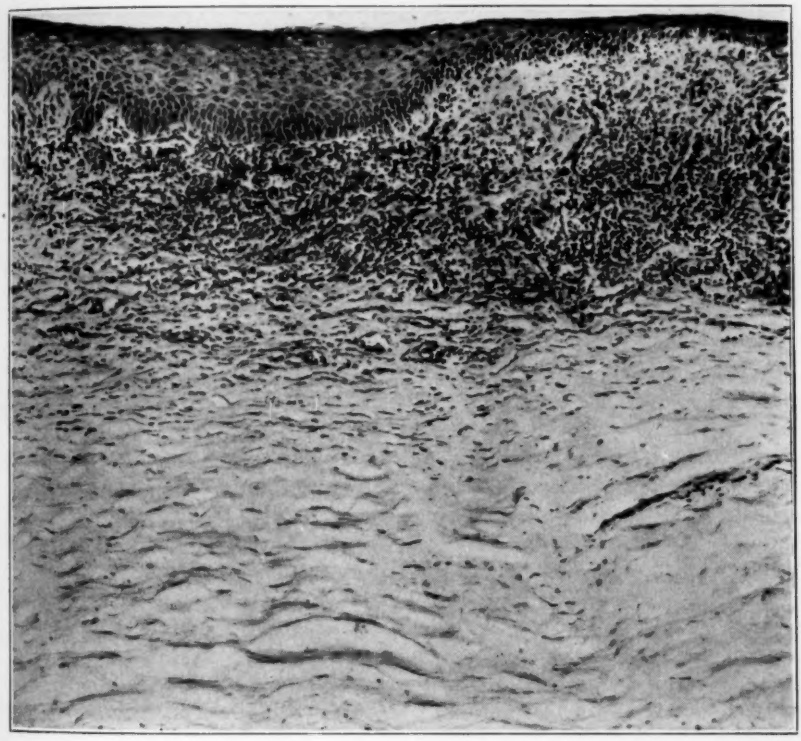


Fig. 2 (case 2).—The cornea (× 95); only two fifths of its thickness is infiltrated.

On January 15 the eye was improved with respect to the condition of the ulcer, but because of ocular hypertension in a painful blind eye, enucleation was performed.

Histopothologic Examination.—The cornea was removed, and sections were stained with hematoxylin and eosin and Gram and Giemsa stains. The epithelium was intact, but Bowman's membrane was destroyed throughout the extent of the ulceration. Here and there pannus degenerativus was present, possibly as a result of the previous secondary glaucoma (figs. 2 and 3). The corneal stroma was infiltrated with many small lymphocytes and a few polymorphonuclear leukocytes. The leukocytic infiltration was confined to the superficial layers of the cornea. Within the lumens of the blood vessels polymorphonuclear leukocytes predominated. Descemet's membrane and the endothelium of the cornea were

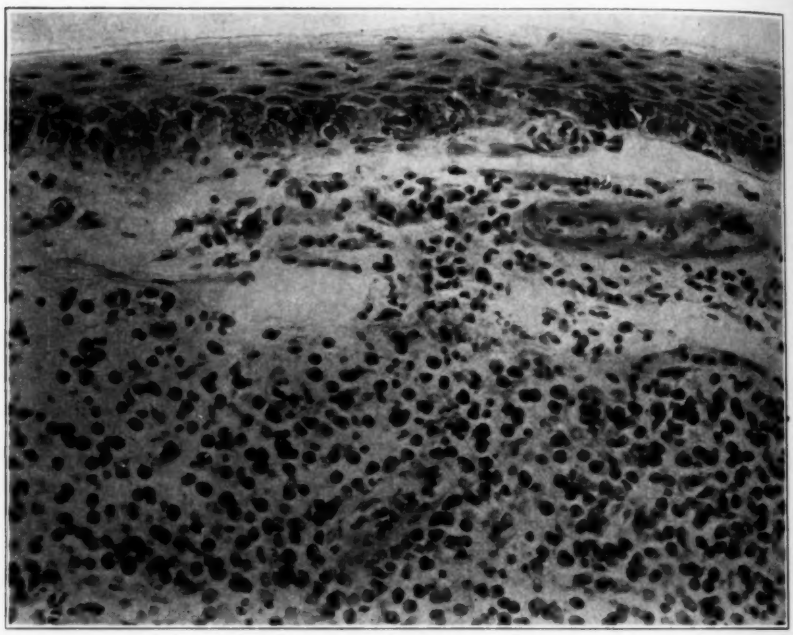


Fig. 3.—Absence of Bowman's membrane. The corneal stroma is infiltrated with small lymphocytes and occasional polymorphonuclear leukocytes, the latter mostly in the blood vessels (× 285).

intact. There was no hypopyon present. A few diplobacilli were seen at the edge of the healing ulcer. The iris showed many plasma cells but no polymorphonuclear leukocytes.

CASE 3.—C. L., aged 48, white, was first seen on Jan. 16, 1940, complaining of pain and redness of the right eye. He stated that ten days prior to admission several foreign bodies had entered the eye and the eye had become progressively more irritated. Five days before admission the patient had observed a minute grayish white area in the lower part of the cornea. This rapidly increased in size to include the entire lower portion of the cornea. A purulent discharge

was present for three days, and the only therapy received was irrigation with boric acid.

On examination slight swelling of the upper and lower eyelids and matting of the lashes with mucopurulent discharge were noted. There was marked conjunctival and circumcorneal injection. A deep ulceration and abscess, measuring 5 by 6 mm., involved the central and inferior portion of the cornea. Adjacent to its margins were irregular areas of superficial corneal ulceration (fig. 4). Adherent to the surface of the central ulcer there was a thick grayish white discharge. The iris was hyperemic, and there were hemorrhagic areas on its anterior surface. The pupil was small. Marked ciliary tenderness was noted, and the intraocular tension was slightly elevated.

Bacteriologic examination of scrapings obtained from the base of the ulcer revealed the diplobacillus of Petit.

A linear keratotomy was performed through the base of the ulcer, with the release of a large plug of necrotic material. The following day the lips of the wound were again spread; however, the necrotic mass rapidly reformed.

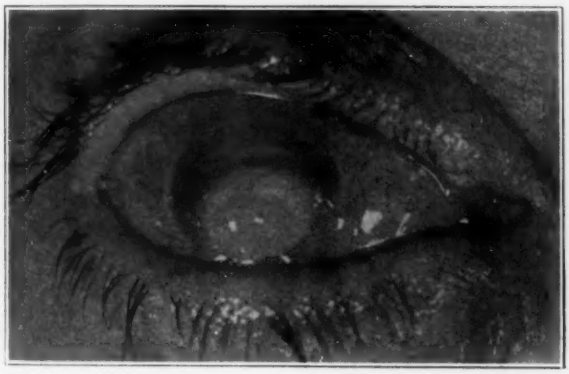


Fig. 4 (case 3).—The extent of the deep ulceration in the center of the cornea.

Local treatment consisted of drops of 0.5 per cent zinc sulfate every four hours and the administration of 0.5 per cent zinc sulfate ointment at night. One per cent atropine sulfate was instilled twice a day, and hot boric acid compresses were applied to the eye three times a day. The lacrimal sac was frequently irrigated with 0.5 per cent zinc sulfate. One application of a thermophore at 158 F. was made to the ulcer for one minute.

Systemic therapy included the administration of 20 grains of sulfanilamide (1.3 Gm.) four times a day for ten days, followed by 15 grains of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) (1 Gm.) four times a day for one week. Two injections of intravenous typhoid were given, one of 5,000,000 and one of 15,000,000 bacteria. General measures were taken to improve the patient's systemic condition.

During the first few days in the hospital there seemed to be improvement in the marginal areas of superficial ulceration. However, there was no alteration in the status of the necrotic central ulcer, and there was no apparent tendency for the ulcer to heal. The pain in and about the eye persisted during the five weeks of treatment. Despite constant atropinization, the pupil became bound down, and

finally the iris was directly adherent to the bulging margins of the abscess, which assumed in one area the appearance of a descemetocele. Because the eye was unsightly and painful and since there was no hope of regaining useful vision, enucleation was performed.

Histopathologic Examination.—In contrast to the second case, only about two fifths of the normal thickness of the cornea remained in the ulcerated area. The epithelium, Bowman's membrane and the superficial three fifths of the cornea had disappeared (fig. 5). The lamellae were separated by an infiltration of polymorphonuclear leukocytes. Marked hypopyon was present, and the iris was adherent to the posterior surface of the cornea.

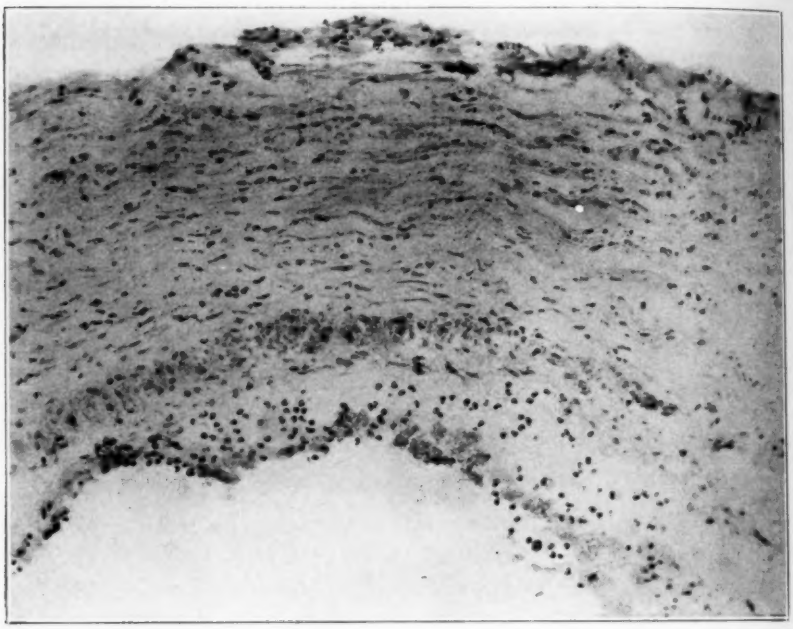


Fig. 5 (case 3).—The upper three fifths of the cornea has ulcerated away; the corneal lamellae are separated by infiltration of polymorphonuclear leukocytes, and hypopyon is present (× 94).

BACTERIOLOGIC STUDY OF THE ORGANISM

Morphologic Characteristics.—The diplobacillus is about 2 to 3 microns long and 1 to 1.5 microns wide, rounded, with slightly thicker ends, and usually occurs in pairs (fig. 6). There is considerable variation in size, the older forms being shorter and broader. It is nonmotile, nonencapsulated and forms no spores. It is gram-negative and nonacid fast. When stained with methylene blue it shows metachromatic granules. The diplobacillus shows a high degree of pleomorphism, especially on chocolate agar medium, where long chains are frequently observed (fig. 7).

Fig. 6.—Morphologic changes after application of Gram's stain to a smear from the corneal ulcer (× 900).

Fig. 7.—Morphologic changes after treating a smear from a culture on chocolate agar with Gram's stain (× 2640).

Cultural Characteristics.—The important features differentiating this organism from the diplobacillus described by Morax and Axenfeld are the ready growth of the diplobacillus of Petit on ordinary laboratory mediums and its ability to liquefy gelatin at room temperature.

Growth on Plain Agar.—The optimal temperature for growth was 37 C., but the bacteria grew at room temperature, at 20 C., fine pinpoint-

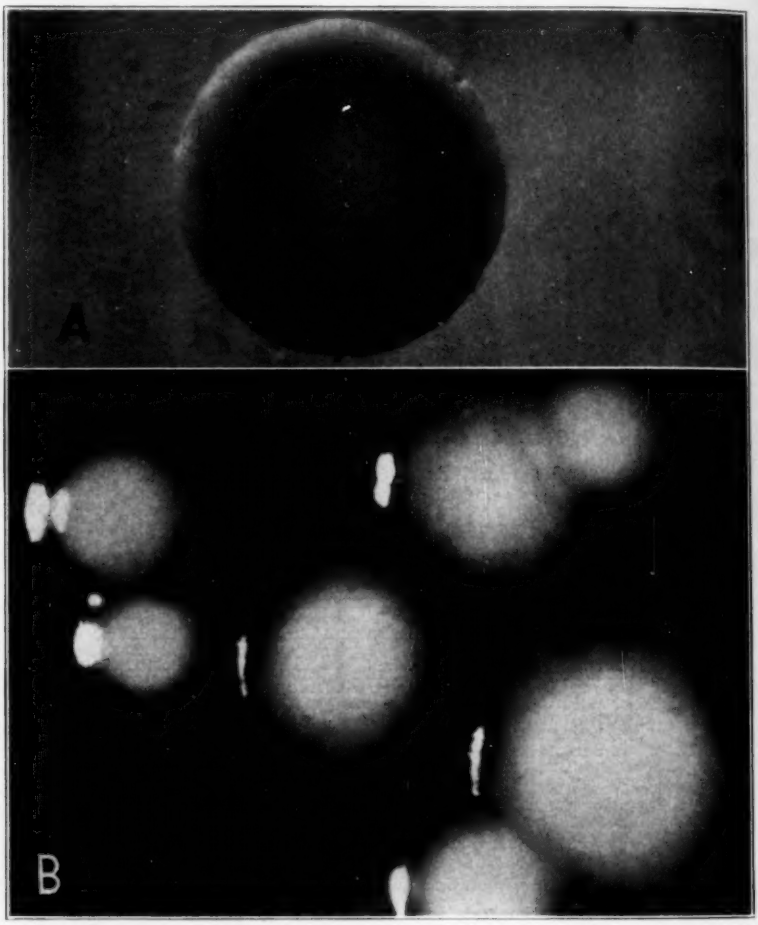


Fig. 8.—Morphologic changes of a colony of the diplobacillus of Petit (× 50). *A*, on plain agar, viewed by transmitted light. *B*, on rabbit blood agar, viewed by lateral illumination.

sized colonies developing in three days. At 37 C. flat, irregular, translucent colonies were formed, 1 to 2 mm. in diameter, in forty-eight hours. The edges were irregular, and there were pronounced mottlings. The colonies were glistening, slightly raised and of watery consistency (fig. 8 *A*). After forty-eight hours' incubation yellowish pigment

appeared. In seven days the mottlings were less noticeable, and in two weeks the edges were smoother and rounder.

Growth on Rabbit's Blood Agar Plates.—Flat, irregular, glistening, translucent, slightly raised colonies were formed with a tendency to flatten at the edges with some roughness and mottlings (fig. 8 *B*). They had a watery consistency, and with longer periods of growth the mottlings

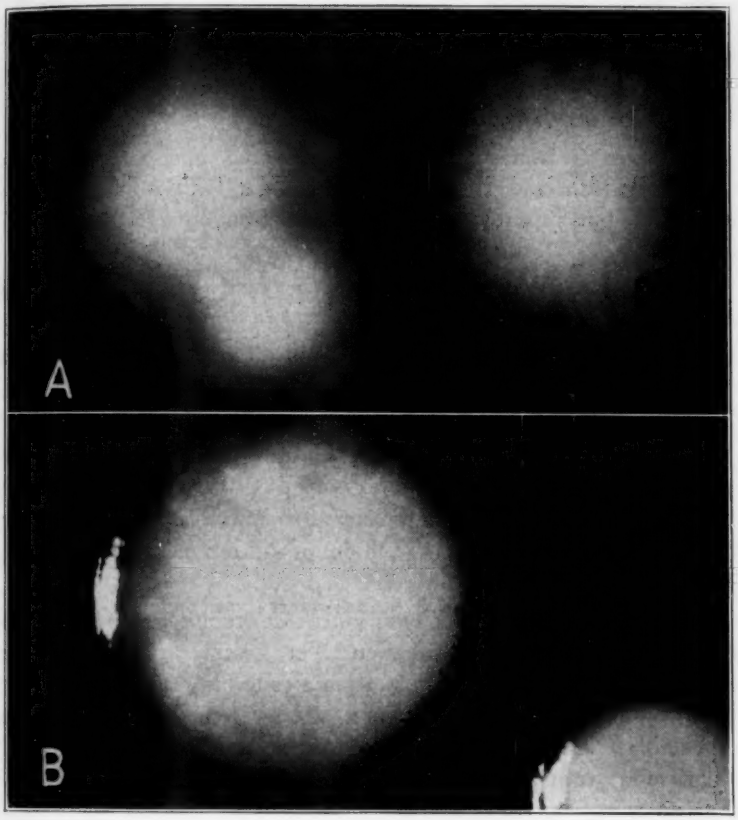


Fig. 9.—Morphologic changes of a colony of the diplobacillus of Petit (× 50). *A*, on sheep's blood agar, viewed by lateral illumination. *B*, on human blood agar, viewed by lateral illumination.

were less and a slight yellowish pigment appeared. There was no hemolysis.

Growth on Sheep's Blood Agar Plates.—The colonies were the same as in the rabbit blood agar plate with the only exception that the colonies had rougher edges (fig. 9 *A*).

Growth on Chocolate Blood Agar Plates.—The colonies were more translucent and delicate, the edges were rougher and the mottlings were larger and spreading. There was some tendency to dissociate.

Growth on Human Blood Agar Plates.—The colonies appeared in forty-eight hours and appeared to be more raised (fig. 9 *B*).

Growth on Dextrose Ascitic Fluid Plates.—The colonies appeared in seventy-two hours, and there were no unusual characteristics.

Growth on Potato and Carrot.—There was a good growth, but no isolated colonies were seen.

Growth on Miller's Medium.—There was a scanty growth in seventy-two hours.

Growth on Gelatin.—Liquefaction occurred in twenty-four hours when the organism was first isolated. Later it failed to liquefy gelatin for a period, but repeated attempts resulted in liquefaction of gelatin again.

Growth on Loeffler's Blood Serum.—In twenty-four hours the serum was liquefied.

Growth in Various Broths.—In plain broth a scanty growth resulted after forty-eight hours' incubation. In rabbit's blood broth there was a moderate growth with a small sediment after prologed incubation. In ascitic fluid broth there was a good growth in twenty-four hours, forming a pellicle layer. On neopeptone broth, p_H 7.7, there was an abundant uniform growth with a slight ring formation on the surface and a moderate amount of sediment. On inulin serum water there was no acid formed or coagulation produced.

Growth Under Anaerobic Conditions.—On rabbit's blood agar plates after twenty-four hours' incubation there were fine pinpoint-sized colonies, which were hardly visible at that time but gradually developed to large colonies in forty-eight hours. The colonies were transparent, grayish and glistening, with central elevation. There was considerable mottling. On plain agar plates there was scanty growth of pinpoint-sized colonies in forty-eight hours. In plain broth there was no growth. In cooked meat medium there was a fairly good growth in forty-eight hours.

Growth in Twenty per Cent Carbon Dioxide.—Good growth resulted in an atmosphere of 20 per cent carbon dioxide tension.

Biochemical Activities.—The diplobacillus grew well on dextrose, lactose, saccharose, salicin, mannitol, maltose and xylose. After two weeks' incubation no acid or gas was formed. Also in litmus milk no acid or gas was formed. Indole was not formed by the Ehrlich reagent on a three day culture in Dunham's peptone. Peptone iron agar produced no iron sulfide. Nitrites were not formed by cultures growing

in a peptone nitrate broth for three days. Neither were proteoses or peptones produced on a four day milk culture. The Voges-Proskauer reaction was negative.

Destruction by Heat.—A broth culture heated at 37 C. for thirty minutes produced a good growth in twenty-four hours after transfer to blood agar plates. A good growth resulted after heating at 45 C. for sixty minutes. The organism grew in two days after heating at 50 C. for sixty minutes. At 56 C. the organism was killed in fifteen minutes (table 1).

TABLE 1.—*Destruction of the Diplobacillus of Petit by Heat*

Temperature	Heating Time, Minutes	Growth After Incubation of One Day
37 C.	15	Good
37 C.	30	Good
45 C.	15	Good
45 C.	30	Good
45 C.	45	Good
45 C.	60	Good
50 C.	15	Good
50 C.	30	20 colonies
50 C.	45	None after 1 day but good in 2 days
50 C.	60	None after 1 day but good in 2 days
56 C.	15	None
56 C.	30	None

TABLE 2.—*Destruction of the Diplobacillus of Petit by Five-Hundredths per Cent Phenolized Saline Solution*

Temperature	Killing Time, Minutes	Growth After Incubation of One Day
20 C.	15	16 colonies
20 C.	30	3 colonies
20 C.	45	None
20 C.	60	None
20 C.	75	None

Destruction by Five-Hundredths per Cent Phenolized Saline Solution.—At 20 C., 3 cc. of broth culture to which 1 cc. of 0.05 per cent phenolized saline solution was added for thirty minutes resulted in a scanty growth (table 2). The organism was killed after being in contact with this solution for forty-five minutes.

EXPERIMENTAL DATA

Corneal Inoculation in Rabbit.—With a 27 gage needle, 0.03 cc. of a saline suspension of living diplobacilli from a twenty-four hour culture of the diplobacillus of Petit on blood serum was injected into the corneal stroma of a rabbit's eye. In twenty-four hours a roughly crescentic abscess of the cornea was present, and there was marked infiltration

of the adjacent corneal stroma with some edema of the whole cornea. The iris was edematous and hyperemic, and a plastic exudate was formed at the pupillary border. The pupil was small. There was a 2 mm. hypopyon. Ciliary injection was prominent. At the end of two days the corneal abscess was larger and the iridocyclitis and hypopyon were at their maximum (fig. 10). The diplobacillus was recovered by culture and smears of the corneal lesion. In three days the inflammatory signs were decreasing in intensity, and by the sixth day the hypopyon had disappeared completely and the inflammatory reaction had markedly subsided.

Serologic Reactions.—An agglutination test with the serum from patient 3 against the diplobacilli isolated from the same patient gave nega-

Fig. 10.—Rabbit eye forty-eight hours after inoculation of cornea with the diplobacillus of Petit.

tive results. This suggests, as would be expected, that the severe corneal involvement was not sufficient to produce antibodies in the blood serum against the diplobacillus.

An immune serum produced by inoculating a rabbit with increasing doses of the diplobacilli from patient 1 agglutinated the diplobacilli from patient 3 in a dilution of 1 to 32, indicating a definite relation between these two strains of diplobacilli.

SUMMARY

Three cases of corneal ulceration are reported in which the diplobacillus of Petit was isolated.

The ulcer is usually gray and centrally located, and the corneal involvement may be both superficial and deep.

Culturally the diplobacillus of Petit can be differentiated from the Morax-Axenfeld diplobacillus by its ready growth on ordinary serum-free mediums and its liquefaction of gelatin at room temperature. The production of long chains on chocolate agar and the presence of metachromatic granules when the culture is stained with methylene blue have been observed with the diplobacillus of Petit used in this study. That the organism can grow under anaerobic conditions has been likewise demonstrated.

Hypopyon keratitis was produced experimentally in the cornea of a rabbit with a culture taken from each of the patients.

Antibodies were not demonstrable in the blood serum of a patient with an extensive infection of the cornea caused by the diplobacillus of Petit.

An immune serum produced by inoculating a rabbit with the diplobacilli from patient 1 agglutinated the diplobacilli from patient 3.

Dr. Phillips Thygeson and Dr. D. Khorazo of the Institute of Ophthalmology of the Presbyterian Hospital supplied valuable aid and suggestions.

PENETRATION OF SULFATHIAZOLE IN THE EYE

JOHN G. BELLOWS, M.D., PH.D.
AND
HERMAN CHINN, PH.D.
CHICAGO

That sulfanilamide and its derivatives have attained a secure position as therapeutic agents for the treatment of certain ocular infections is attested by numerous reports. Of these, sulfanilamide (paraaminobenzenesulfonamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfathiazole (2-sulfanilamidothiazole) have been employed most extensively. Experimental justification for the use of sulfanilamide and sulfapyridine in the eye lies in the ready penetration of these compounds into the ocular tissues and fluids in concentrations approximating that of the blood.[1] Thus far, despite the clinical use of sulfathiazole, no experimental evidence has been presented to show that it reaches the eye. If this drug shows a penetrability similar to that of the other two it should prove a valuable adjunct in ocular therapy. It is superior to sulfapyridine in its ready intestinal absorption and is less toxic.[2] Nausea and vomiting are less than with sulfapyridine, although dermatitis is more frequently encountered.[3] Experimentally its effectiveness is equal to or greater than that of sulfapyridine against certain types of pneumococci,[4] the meningococcus,[4a] the beta hemolytic streptococcus,[4]

From the Departments of Ophthalmology and Physiological Chemistry, Northwestern University Medical School.

1. Bellows, J. G., and Chinn, H.: Distribution of Sulfanilamide in the Eye, J. A. M. A. **112**:2023 (May 20) 1939. Chinn, H., and Bellows, J. G.: The Distribution of Sulfanilyl 2-Aminopyridine in the Body, J. Lab. & Clin. Med. **25**: 735, 1940.

2. van Dyke, H. B.; Greep, R. O.; Rake, G., and McKee, C. M.: Observations on Toxicology of Sulfathiazole and Sulfapyridine, Proc. Soc. Exper. Biol. & Med. **42**:410, 1939. Long, P. H.; Haviland, J. W., and Edwards, L. B.: Acute Toxicity, Absorption and Excretion of Sulfathiazole and Certain of Its Derivatives, ibid. **43**:328, 1940. Reinhold, J. G.; Flippin, H. F., and Schwartz, L.: Observations on Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**: 393, 1939.

3. Spink, W. W., and Hansen, A. E.: Sulfathiazole: Clinical Evaluation, J. A. M. A. **115**:840 (Sept. 7) 1940.

4. (*a*) McKee, C. M.; Rake, G.; Greep, R. O., and van Dyke, H. B.: Therapeutic Effect of Sulfathiazole and Sulfapyridine, Proc. Soc. Exper. Biol. & Med.

(Footnote continued on next page)

Bacillus proteus,[5] Staphylococcus aureus,[6] Streptococcus faecalis[7] and the gonococcus.[4c]

Sadusk, Blake and Seymour[8] found sulfathiazole to be readily absorbed after oral administration and to diffuse rapidly into the pleural and ascitic fluids. However, none or only traces of the drug entered the spinal fluid. This observation suggests that oral administration is of questionable value in the treatment of meningitis. Since the composition of the aqueous humor is similar to that of the spinal fluid, it was thought important to ascertain whether sulfathiazole reaches the fluids and tissues of the eye in sufficient concentration to be of value in ocular infections.

EXPERIMENTS

Two-tenths gram of sulfathiazole (supplied by the Winthrop Chemical Co., Inc.) per kilogram of body weight was suspended in 15 to 20 cc. of water and administered by stomach tube to dogs under pentobarbital sodium anesthesia. At specified intervals from one to twenty-four hours afterward, aqueous humor, blood and cerebrospinal fluid were removed and analyzed according to the modification by Bratton and Marshall[9] of the original method of Marshall, Emerson and Cutting.[10] Since preliminary tests indicated that the highest concentration of the sulfathiazole was reached after four to six hours, the eyes were removed at these times and the constituent tissues analyzed in the manner previously described.[1] A similar procedure was adopted

---

42:417, 1939. (*b*) Long, P. H., and Bliss, E. A.: Bacteriostatic Effects of Sulfathiazole upon Various Microorganisims: Its Therapeutic Effects in Experimental Pneumococcal Infections, ibid. **43**:324, 1940. (*c*) Lawrence, C. A.: Bacteriostatic Actions of Three Thiazole Derivatives of Sulfanilamide on Bacteria in Broth Culture, ibid. **43**:92, 1940.

5. (*a*) Helmholz, H. F.: Bactericidal Effect of Sulfathiazole and Sulfamethylthiazole in Bacteria Found in Urinary Infections, Proc. Staff Meet., Mayo Clin. **15**:65, 1940. (*b*) Hill, J. H.: Comparative in Vitro Action of Sulfanilamide, Sulfapyridine and Sulfathiazole in Urine, J. Urol. **43**:491, 1940. (*c*) Long and Bliss.[4b]

6. Rake, G., and McKee, C. M.: Action of Sulfathiazole and Sulfamethylthiazole on Staphylococcus Aureus, Proc. Soc. Exper. Biol. & Med. **43**:561, 1940. Rammelkamp, C. H., and Keefer, C. S.: Sulfathiazole: Effect on Staphylococcus Aureus in Vitro, ibid. **43**:664, 1940. Long and Bliss.[4b] Hill.[5b]

7. Helmholz.[5a] Hill.[5b]

8. Sadusk, J. F.; Blake, F. G., and Seymour, A.: Observation on Absorption, Excretions, Diffusion and Acetylation of Sulfathiazole in Man, Yale J. Biol. & Med. **12**:681, 1940.

9. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537, 1939.

10. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide; Absorption and Excretion; Method of Determination in Urine and Blood, J. A. M. A. **108**:953 (March 20) 1937.

with another series of dogs, but the sulfathiazole was dissolved in hydrochloric acid before administration. The results of these experiments are listed in table 1.

The concentration of sulfathiazole in the blood and in the tissues of the eye is markedly increased by giving the drug in its dissolved state. Thus, after four hours a value of 7.4 mg. per hundred cubic centimeters of blood was attained in dogs receiving sulfathiazole in hydrochloric acid, whereas the concentration was only 1.7 mg. per hundred cubic centimeters in dogs given the suspended material. The concentration in the tissues of the eye likewise showed an increase, but of lesser magnitude. A slight difference between these two groups was also noted in the time taken for maximum concentration in the blood, the maximum figure

TABLE 1.—*Sulfathiazole in Tissues and Fluids After a Large Dose*

	Dissolved in Hydrochloric Acid Before Oral Administration					Aqueous Suspension Given Orally				
	1 Hr.	2 Hr.	4 Hr.	6 Hr.	24 Hr.	1 Hr.	2 Hr.	4 Hr.	6 Hr.	24 Hr.
Blood *	3.5	5.8	7.4	6.8	1.9	0.8	1.3	1.7	2.0	2.1
Aqueous humor	0.0	0.1	0.4	0.0	0.7	0.0	0.1	0.3	0.1	0.0
Cerebrospinal fluid	0.0	0.0	1.0	0.0	1.4	0.0	0.1	0.0	0.1	0.0
Lens			0.0	0.0				0.0	0.0	
Cornea			2.0	2.0				0.0	0.3	
Sclera			10.4	4.6				...	2.5	
Chorioretinal layer			4.9	2.7				1.7	2.4	
Vitreous humor			0.9	0.4				0.2	0.4	
Conjunctiva			8.4	8.6				2.9	2.6	

* The concentration of the drug in the blood, cerebrospinal fluid and aqueous humor is expressed in milligrams per hundred cubic centimeters. In all other tissues it is expressed in milligrams per hundred grams of moist tissue.

being attained within four hours in the group receiving the drug in acid and after approximately six hours in the group receiving the nonacidified sulfathiazole.

The most significant finding in each group was the failure of sulfathiazole to penetrate into the aqueous humor, vitreous humor or spinal fluid in appreciable quantities. In practically every case less than 0.5 mg. per hundred cubic centimeters could be detected in these fluids, and in most cases less than 0.1 mg. per hundred cubic centimeters. Thus, four hours after the drug was ingested the blood showed 7.4 mg. per hundred cubic centimeters, while only 0.4 mg. per hundred cubic centimeters was present in the aqueous humor and 1 mg. per hundred cubic centimeters in the spinal fluid.

The lens, which is nourished exclusively by the surrounding media, contained no sulfathiazole at any time. The cornea showed small amounts, with the more vascular uveal, retinal and conjunctival tissues containing a somewhat higher concentration. For some unknown reason the scleral tissue uniformly had the highest concentration of sulfathiazole, in some instances actually exceeding that of the blood during a particular time interval.

A comparison is made in table 2 of the levels in the various fluids and tissues of the several drugs after the administration of 0.2 Gm. per kilogram of body weight. It can be seen that the values of sulfathiazole in the blood compare favorably with those of sulfapyridine. In every case, however, with the single exception of the scleral tissue, the concentration of sulfapyridine exceeded that of sulfathiazole in the eye and in the spinal fluid. For example, four hours after administration the following concentrations were determined in the aqueous humor: 10.9 mg. of sulfanilamide, 5.8 mg. of sulfapyridine but only 0.4 mg. of sulfathiazole, per hundred cubic centimeters.

TABLE 2.—*Comparative Concentration* of Sulfanilamide Drugs Four Hours After Oral Administration*

	Sulfanilamide	Sulfapyridine	Sulfathiazole
Blood	18.0	6.1	7.4
Aqueous humor	10.9	4.9	0.4
Vitreous humor	8.4	5.8	0.9
Spinal fluid	...	3.9	1.0
Cornea	13.4†	6.8	2.0
Sclera	....	7.0	10.4
Chorioretinal tissue	15.2	6.3	4.9
Lens	2.7	1.1	0.0

* The concentration of the drugs in the blood, cerebrospinal fluid and aqueous humor is expressed in milligrams per hundred cubic centimeters. In all other tissue it is expressed in milligrams per hundred grams of moist tissue.

† This value is for the cornea and the sclera combined.

COMMENT

The clinical value of sulfathiazole may be enhanced when it is given with hydrochloric acid to ensure more rapid absorption. This precaution should be of particular importance when the drug must be given to achlorhydric patients.

The inability of more than traces of sulfathiazole to enter the avascular tissues and the fluids of the eye indicates that the value of this compound in ocular infections is decidedly limited. These data suggest that sulfathiazole would be ineffective in endogenous and exogenous infections of the ocular media. On the other hand, justification exists for its use in infections of the uveal, retinal and conjunctival tissues by the aforementioned organisms. So far as we know there has been no report of its use in trachomatous infection.

SUMMARY AND CONCLUSIONS

The concentration of sulfathiazole in the blood and spinal fluid and in the various ocular tissues and fluids of the dog has been determined one, two, four, six and twenty-four hours after oral administration of 0.2 Gm. per kilogram of body weight. The maximum concentration was reached from the fourth to the sixth hour.

Higher values were obtained consistently when sulfathiazole was given dissolved in hydrochloric acid than when it was given in an aqueous suspension.

Only traces of sulfathiazole were found in cerebrospinal fluid, aqueous humor, lens, cornea and vitreous humor. The other tissues examined, in descending order of concentration, were sclera, conjunctiva and the chorioretinal layer.

A comparison has been made of the concentrations in these tissues of sulfanilamide, sulfapyridine and sulfathiazole similarly administered.

The clinical implications of these results are discussed.

Prof. S. R. Gifford suggested this problem, and Prof. C. J. Farmer gave helpful suggestions and criticism.

ACUTE RETROBULBAR NEURITIS AS A MANIFESTATION OF ACUTE LOCALIZED TISSUE ANOXIA

TREATMENT WITH VASODILATORS

WALTER F. DUGGAN, M.D.
UTICA, N. Y.

Acute retrobulbar neuritis is a disease of the optic nerve, chiasm or tract usually characterized by marked and sudden loss of sight in one or both eyes, with a central or paracentral scotoma. Rarely the fields are contracted. Occasionally there is pain on movement of the eye. The pupil often shows hippus. The fundus may be normal, or there may be venous congestion, optic neuritis or papilledema of as much as 6 D. When the lesion is close to the globe the changes in the disk are pronounced and the condition is called optic neuritis. When the lesion is behind the entrance of the retinal vessels into the optic nerve the fundus is usually normal and the condition is called retrobulbar neuritis. Although the two conditions are treated as separate and distinct diseases in the textbooks, the differences between acute optic and acute retrobulbar neuritis are quantitative rather than qualitative and are due only to the site and the size of the lesion. No useful purpose is served by separating the two conditions. They are essentially the same disease. True optic neuritis involving only the nerve fibers on the disk anterior to the lamina cribosa is almost impossible; so optic neuritis in every case probably has a retrobulbar component. The reverse is not necessarily true.

The extent of visual loss depends on the location and the number of nerve fibers involved by the acute lesion. If the papillomacular bundle is involved, a small lesion can cause marked depression of visual acuity. If this bundle is not involved, there may be a large scotoma with normal visual acuity.

The scotoma for white depends on the position and size of the lesion. When it is close to the lamina cribosa, an arcuate, or ring, type scotoma is often found; when it is farther back in the optic nerve, various types of central or paracentral scotoma occur; when it is

---

An original contribution in ophthalmology presented anonymously and awarded the Lucien Howe Prize in 1940.

located in the optic chiasm, bilateral paracentral or cecocentral scotomas result, and when it is in the optic tract, homonymous defects are found.

In addition to the scotoma for white, there is always a scotoma for colors, larger for red and green than for blue and yellow. The scotoma for red and green is the first to appear and the last to disappear during the evolution and involution of the lesion.

ETIOLOGY

Acute retrobulbar neuritis has been ascribed to allergy, focal infection, pregnancy, lactation, endocrine disorders, multiple sclerosis and many other conditions. At present I do not wish to consider symptomatic conditions due to tumor of the brain, metastatic tumors or injury. Neither do I wish to consider so-called chronic retrobulbar neuritis due to tobacco, avitaminosis or pernicious anemia. The chronic conditions develop slowly, attaining their most marked effects in weeks or months. Acute retrobulbar neuritis develops with devastating rapidity, so that the height of visual loss occurs in a few hours or, less often, in a few days, after which the condition may slowly improve.

Acute retrobulbar neuritis, in addition to existing solely as an ophthalmologic disease, may occur (1) as a prominent and frequent manifestation of the demyelinating diseases and (2) as an unusual complication of many other conditions, including acute anterior poliomyelitis,[1] septic wounds,[2] apiol poisoning,[3] pregnancy,[4] ventriculography,[5] carbon sulfide poisoning,[6] serous meningitis [7] and endocrine disturbances,[8] as well as a donor following the giving of blood.[9] Lillie [10] reported cases in which it was due to multiple sclerosis, Schilder's disease and lactation. Snell [11] reported cases in which it was due to mixed foci of infection, pneumonia, tuberculosis, urethritis, multiple sclerosis and surgical trauma (in the last case acute amaurosis developed on the day after a sinus was opened). The condition has been ascribed to chronic

1. Much, V., and Hüppi, A.: Klin. Monatsbl. f. Augenh. **93**:333 (Sept.) 1934.
2. Butler, T. H.: Brit. J. Ophth. **10**:184 (April) 1926.
3. Juhasz-Schäffer, A.: Klin. Wchnschr. **11**:1232 (July 16) 1932.
4. Kagan, Y. A.: Sovet. vestnik oftal. **5**:503, 1934.
5. Masson, C. B.: Bull. Neurol. Inst. New York **3**:190 (June) 1933.
6. Monbrun, A.; Richet, C., and Facquet, J.: Arch. d'opht. **49**:697 (Nov.) 1932.
7. Puscariu, E.: Brit. J. Ophth. **21**:599 (Nov.) 1937.
8. Thies: Klin. Monatsbl. f. Augenh. **88**:855 (June) 1932; abstracted, Arch. Ophth. **9**:500 (March) 1933.
9. Duggan, W. F.: Use of Vasodilators in Treatment of Retrobulbar Neuritis, Arch. Ophth. **16**:380 (Sept.) 1936.
10. Lillie, W. I.: Am. J. Ophth. **17**:110 (Feb.) 1934.
11. Snell, A. C.: New York State J. Med. **33**:370 (March 15) 1933.

tonsillar infection [12] and to suppurative sphenoiditis.[13] Feigenbaum and Salzberger [14] reported 24 cases, in most of which the condition occurred after an epidemic of influenza. In 16 cases the sphenoid and the posterior ethmoid sinuses were opened. Eight of the patients operated on and 3 of those not operated on were cured.

The condition has been reported as following prophylactic vaccination against rabies [15] and following combined inoculations against typhoid, cholera and dysentery.[16] A vascular origin was suggested in the last case.

Clay and Baird [17] reported 7 cases of this condition (acute in 6 and old in 1), in 6 of which there was bilateral involvement. In the acute conditions there was papilledema of from 1 to 6 D. On very insufficient evidence these authors attributed the condition in their cases to a virus.

The disease has occurred after poisoning by trichloroethylene.[18] Bucy [19] reported a case in which it was due to sulfanilamide, and I have recently been informed of another case of this kind. Also, in July 1939 I saw a boy of 7 years who had bilateral optic neuritis and paralysis of one external rectus muscle following the taking of sulfapyridine. In 1 case which came to my attention a woman had been stung by a hornet ten days before the onset of loss of sight. In another case the patient was receiving injections for immunization against poison ivy. I have also observed several cases in which the disease was due to hemorrhage, and many similar cases have been reported.[20]

---

12. Wilson, G., and Darkes, W. F.: Unilateral Choked Disk Due to Chronic Tonsillar Infection, J. A. M. A. **100**:1233 (April 22) 1933. Harry, P. A.: Brit. J. Ophth. **6**:216 (May) 1922.

13. Bulson, A. E.: Choked Disk (Papilledema) Due to Disease of Sphenoidal Sinus, J. A. M. A. **97**:926 (Sept. 26) 1931.

14. Feigenbaum, A., and Salzberger, M.: Folia oto-laryng. orient. **1**:50 (Oct.) 1932.

15. Cormack, H. S., and Anderson, L. A. P.: Brit. J. Ophth. **18**:167 (March) 1934. Hasabe: Acta Soc. ophth. japon. **38**:102 (July) 1934. Suzuki: ibid. **39**: 219, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **36**:415, 1936.

16. Shannon, C. E. G.: Bitemporal Paracentral Scotoma, Arch. Ophth. **6**:544 (Oct.) 1931.

17. Clay, G. E., and Baird, J. M.: Unclassified Type of Optic Neuritis: Report of Cases, Arch. Ophth. **18**:777 (Nov.) 1937.

18. Isenschmid, R., and Kunz, E.: Schweiz. med. Wchnschr. **65**:530 (June 8) 1935.

19. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

20. (*a*) Barr, A. S.: Am. J. Ophth. **17**:396 (May) 1934. (*b*) Knapp, A.: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Co., 1918, pp. 407-409. (*c*) Moore, R. F.: Medical Ophthalmology, ed. 2, London, J. & A. Churchill, 1925, pp. 109-111.

Besso [21] reported the occurrence of this condition in a syphilitic patient after the administration of 2 Gm. of potassium iodide within twenty-four hours. The patient also showed iodism, orbital edema with exophthalmos, dacryoadenitis and corneal infiltration. When the fundi could be examined, there was marked atrophy of the optic nerve. Besso attributed the loss of sight to the extreme exophthalmos and to compression of the vessels in the orbit. It is just as probable that the patient had intense edema of the optic nerves which is the basic pathologic change associated with acute retrobulbar neuritis.

Kahoun [22] reported a case in which optic neuritis and paralysis of the extraocular and the levator muscles developed after the patient breathed large amounts of carbon monoxide. This case is cited because the patient suffered from an anemic anoxemia, similar in many ways to the anemic anoxemia following hemorrhage. The ocular findings can be interpreted as due to a localized tissue anoxia superimposed on an anemic anoxia.

With regard to the sinal origin of acute retrobulbar neuritis, a brief survey of the recent literature revealed the interesting fact that sixteen writers were in favor of the sinal origin of acute retrobulbar neuritis, eleven stated the belief that the sinuses play no part in its production, and three, Bedell,[23] Campbell [24] and Hoople,[25] favored operation only if there was definite purulent sinusitis. Moore [26] expressed definite opposition to the theory of a sinal origin, and Benedict [27] expressed the opinion that operations on the sinuses are nonspecific in their mode of action. I agree with the last five authorities cited.

PATHOLOGIC PICTURE

Examination of the optic nerve in the acute stage of retrobulbar neuritis is rarely possible. However, in autopsy reports of cases of neuromyelitis optica the pathologic change in the optic nerves has been described as consisting of localized areas of softening and necrosis with perivascular lymphocytic infiltration. The myelin sheaths show swelling or disintegration. One may say that the lesion is strictly

21. Besso, M. G.: Rassegna ital. d'ottal. **6**:381 (July-Aug.) 1937; abstracted, Am. J. Ophth. **21**:341 (March) 1938.

22. Kahoun, S.: Československ. opht. **3**:122, 1937; abstracted, Am. J. Ophth. **21**: 340 (March) 1938.

23. Bedell, A.: New York State J. Med. **33**:361 (March 15) 1933.

24. Campbell, E. H.: Relationship of Sinusitis to Optic and Retrobulbar Neuritis, with Special Reference to Etiology and Treatment, Arch. Ophth. **16**:236 (Aug.) 1936.

25. Hoople, G. D.: New York State J. Med. **33**:365 (March 15) 1933.

26. Moore,[20c] p. 166.

27. Benedict, W. L.: Retrobulbar Neuritis and Disease of Nasal Accessory Sinuses, Arch. Ophth. **9**:893 (June) 1933.

perivascular with transudation of plasma ("liquor-stasis") and passage of lymphocytes ("leukostasis") into the perivascular spaces. Ricker first used the foregoing terms in his monograph "Sklerose und Hypertonie der innervierten Arterien" and pointed out that changes in the permeability of the capillaries can account for the passage of plasma, white cells and even red cells into the perivascular tissues.

Old lesions, especially of multiple sclerosis, reveal sclerotic plaques, glial in origin, around arterioles the walls of which are thickened, or the arterioles may be obliterated. The nerve fibers show loss of their myelin sheaths.

The pathologic picture in cases of the acute condition can be interpreted as the result of an arteriolar spasm, with dilatation and increased permeability of the capillaries. The arteriolar spasm limits the access of oxygen to the capillaries; because of the anoxia the capillaries become more permeable, which leads to edema and round cell infiltration, and the tissues supplied by the capillaries show a loss of function due to lack of available oxygen. If the anoxia is of sufficient duration or intensity necrosis occurs and an infarct forms. The healed condition shows the ingrowth of glial cells around the damaged arteriole and capillaries, just as connective tissue develops in an infarct outside of the nervous system.

In other words, acute retrobulbar neuritis is due to an acute vascular catastrophe in the optic nerve, characterized by arteriolar spasm and increased capillary dilatation and permeability leading to localized edema, tissue anoxia and loss of function in the involved tissue.

Whether the capillary changes or the arteriolar spasm is primary is debatable and not important. It is known that lack of oxygen can cause the capillary changes (Landis), and it is also known that excessive and prolonged arteriolar constriction, such as is produced by overdoses of epinephrine, can produce changes in the capillary permeability by so limiting the access of blood to the capillaries that both they and the tissues they supply suffer from anoxia. Moreover, in cases of acute localized tissue anoxia all examinations of the blood may give normal results, since localized anoxia can exist without anoxemia.

PROGNOSIS

The prognosis is said to be good, even if no treatment is given. Every ophthalmologist has probably encountered at least 1 case in which this was true. However, atrophy of the optic nerve with decreased visual acuity is due in many cases to an attack of acute retrobulbar neuritis which did not completely resolve. As I shall later prove, in many of these cases the patients do not tend to recover economically useful vision even with the methods of therapy in vogue.

TREATMENT

It is customary to order various examinations, both clinical and laboratory, in cases of acute retrobulbar neuritis. The supposition is that this condition is always secondary to disease elsewhere in the body and that if even borderline pathologic change is found outside the visual system it is the cause and must be treated.

A "complete" work-up contributes very little to the treatment of acute retrobulbar neuritis. For example, in Clay and Baird's [17] cases the 7 patients were subjected to fifty-two laboratory procedures. All gave negative results. In addition, general physical, aural, nasal, pharyngeal and neurologic examinations were done. All gave negative results. Six of the patients were hospitalized for at least three weeks (as nearly as could be determined from the case reports). Treatment consisted of injections of foreign protein, limitation of fluids and, in a few cases, saline catharsis. In one eye an attack occurred while the patient was receiving the aforementioned treatment! The only information of any significance in the history was the fact that 6 of the patients had had a head cold or grip four to fourteen days before the onset of the attack. Their conditions differed from the usual form of the disease only in that there was marked papilledema with the acute neuritis. However, since the presence or absence of papilledema depends only on the location of the lesion in the optic nerve, I do not think that their cases belong in a different category, nor do I think it necessary to assume a virus origin until more knowledge as to the nature of viruses is available.

I have observed or heard of cases of acute retrobulbar neuritis in which the patients have been subjected to a barrage of operations (on sinuses, tonsils and teeth), to fever therapy, to the administration of sulfanilamide and to diathermy. Large amounts of vitamins, potassium iodide and other drugs have been given. In some instances hospital beds have been utilized for weeks. The visual results have not been striking. It seems to me that last resort operations, born of desperation and fathered by tradition, can be eliminated from the therapeutic armamentarium. Even if a patient has a questionable focus of infection, relief of symptoms following surgical treatment of the focus is no proof that the focus is the cause of the lesion. Foci of infection should be eliminated, surgically or otherwise, only if there is enough infection or pathologic change in the foci themselves to require intervention, not because their removal might influence the involution of an acute angiospastic lesion in some remote part of the body.

Reimann and Havens,[28] in a comprehensive review of the evidence for and against focal infection, stated: "In the light of present knowl-

28. Reimann, H. A., and Havens, W. P.: Focal Infection and Systemic Disease: A Critical Appraisal, J. A. M. A. **114**:1 (Jan. 6) 1940.

edge, the removal of such local infections in the hope of influencing remote or general symptoms and disease must still be regarded as an experimental procedure not devoid of hazard."

If acute retrobulbar neuritis is due to arteriolar spasm and to increased capillary dilatation and permeability and if the pathologic and functional changes are due to anoxia, the condition should respond to intensive vasodilator therapy. The only purpose of vasodilator therapy is to improve the blood supply to the tissues, thereby relieving the tissue anoxia. This type of therapy is logical and is based on the pathologic physiology of the acute condition. And as Moon [29] has stated, "Many phenomena called toxic are essentially anoxic."

I. DATA ON CONTROL SERIES OF PATIENTS NOT TREATED WITH VASODILATORS

A statistical survey was made of 48 clinic patients who had suffered fifty-four attacks of acute retrobulbar neuritis involving 65 eyes between 1907 and 1936. In 31 patients 1 eye was involved once; in 11 patients both eyes were involved simultaneously, and in 6 patients both eyes were involved at different times. Twenty-one (43 per cent) of the patients were Jewish, and 14 (29 per cent) were of Anglo-American stock.

Sex and Age.—There were 32 males. Their ages ranged between 17 and 61 years, and the average age was 37.3 years. There were 16 females. Their ages ranged between 15 and 60 years, and the average age was 34.8 years. Twenty of the men and 10 of the women were between 23 and 46 at the time of their first attack.

Some of these patients were followed and treated; others were seen once shortly after the acute attack but failed to return for observation, and the remainder were seen some time after the acute attack had subsided, so that the diagnosis depended on the history plus the presence of atrophy of the optic nerve. Two had multiple sclerosis; 1 later had myasthenia gravis; 1 had syphilis; 1 had peripheral neuritis, and 1 gave a history of two transient attacks of hemiplegia.

Therapy varied and was usually nonspecific; so only the patients who had been subjected to operations on the sinuses have been grouped separately. The visual results in the 65 eyes are recorded in table 1.

Anaylsis of Table 1.—A. Eyes Seen Only Once (Columns 1, 2 and 3): In column 1 are given the visual findings for 12 eyes seen during the first month after an attack of acute retrobulbar neuritis; 75 per cent of the eyes had vision of 20/100 or less, and 50 per cent of the eyes had vision of 5/200 or less.

29. Moon, V.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

TABLE 1.—*Visual Results in Sixty-Five Eyes Treated Otherwise Than with Vasodilators or Not Treated*

	A			B						C	D
	37 Eyes Seen Once			28 Eyes Treated and Followed						13 Eyes Treated by Nasal Surgery	Total of 65 Eyes
	1	2	3	4	5	6	7	8	9	10	11
				20 Eyes Treated Without Nasal Surgery		8 Eyes Treated With Nasal Surgery				Includes 5 Cases from Column 3 Which Were Not Improved and 8 Cases from Columns 6 and 7	
Vision	12 Eyes Seen 3 to 30 Days After Onset	25 Eyes Seen 35 Days to 28 Years After Onset	Total (37 Eyes)	Before Rx	After Rx	Before Rx	After Rx	Total of Columns 4 and 6 Before Rx	Total of Columns 5 and 7 After Rx	Final Visions	Final Visions Columns 3 and 9
0 to 5/200.....	6	14	20 (54.1%)	7	4	2	..	9 (32.1%)	4 (14.3%)	4 (30.8%)	24 (37 %)
6/200 to 20/200.	1	6	7 (18.9%)	7	6	5	1	12 (42.9%)	7 (25 %)	1 (7.7%)	14 (21.5%)
20/100.....	2	..	2 (5.4%)	1	1	..	..	1 (3.6%)	1 (3.6%)	1 (7.7%)	3 (4.6%)
20/ 70.....	..	2	2 (5.4%)	1	1	1	..	2 (7.1%)	1 (3.6%)	.....	3 (4.6%)
20/ 50.....	1	..	1 (2.7%)	2	2	..	..	2 (7.1%)	2 (7.1%)	.....	3 (4.6%)
20/ 40.....	..	1	1 (2.7%)	1	1	..	1	1 (3.6%)	2 (7.1%)	1 (7.7%)	3 (4.6%)
20/ 30.....	2	2	4 (10.8%)	..	2	..	2	.....	4 (14.3%)	2 (15.4%)	8 (12.3%)
20/ 20.....	..	..	.....	1	3	..	3	1 (3.6%)	6 (21.4%)	3 (23.0%)	6 (9.2%)
Improved vision not stated	..	..	.....	..	..	..	1	.....	1 (3.6%)	1 (7.7%)	1 (1.5%)
Unchanged or worse after treatment	..	..	.....	..	9	..	1	.....	10 (35.7%)	6 (46.2%)	10 (15.4%)
Atrophy of the optic nerve	2	16	18 (48.6%)	..	4	..	1	.....	5 (17.9%)	5 (38.4%)	23 (35.4%)

Column 5. Average time of improvement per eye for 8 improved eyes: 45 days
Column 7. Average time of improvement per eye for 6 improved eyes: 21 days
Column 9. Average time of improvement per eye for 14 improved eyes: 34.3 days

In column 2 are given the findings for 25 eyes seen from thirty-five days to twenty-eight years after the attack. Many of the patients had been treated elsewhere at the time of the attack, yet 80 per cent had vision of 20/200 or less and 56 per cent had vision of 5/200 or less. In addition, 64 per cent of the eyes showed atrophy of the optic nerve.

In column 3 are given the visual findings for the 37 eyes which were seen but once. In 78.4 per cent of the eyes the vision varied between total blindness and 20/100. Only 4 eyes (10.8 per cent) had economically useful vision (20/30), and 18 eyes (48.6 per cent) had atrophy of the optic nerve.

If acute retrobulbar neuritis has a great natural tendency to heal spontaneously, one should be able to expect better visual results than those listed in columns 2 and 3.

B. Eyes Treated and Followed: In columns 8 and 9 are given the visual results for 28 eyes, before and after treatment. Before treatment, 22 eyes (78.6 per cent) had vision of from perception of hand movements to 20/100. After treatment, 10 eyes (35.7 per cent) had vision of from 20/30 to 20/20. Ten eyes (35.7 per cent) showed no change or became worse during treatment.

Columns 4 and 5 give the visual results for 20 eyes treated without nasal operation, and columns 6 and 7 give the visual results for 8 eyes of patients for whom nasal operation was the principal therapy. While some preference might be indicated for nasal operation from these figures, the differences are not so marked if all the cases in which the condition was treated by sinal operation are analyzed (see next section).

C. Visual Results in Patients Treated with Nasal Operation: In column 10 are given the final visions for 13 eyes in cases in which a nasal operation was the major therapeutic agent. In 6 instances the ethmoid sinuses were opened. For the other 7 eyes, there were no available data as to which sinus was opened. Five of these eyes (column 3) were seen some time after the operation; the results in the other 8 eyes are from columns 6 and 7.

After operation, 6 eyes (46.2 per cent) had vision of from perception of hand movements to 20/100. Five eyes (38.4 per cent) had vision of from 20/30 to 20/20. Moreover, 6 eyes (46.2 per cent) were apparently unchanged or worse after this treatment, and in 5 eyes there was atrophy of the optic nerve.

While only a few eyes were treated in this manner, it is apparent that the percentage of eyes which were relatively unimproved is not materially different than that for the cases in which surgical therapy was not given (column 7). The percentage of patients attaining vision of 20/30 or better is slightly higher for the patients who were operated on (column 10). However, if 1 more patient had attained vision of 20/30 without surgical intervention and if 1 patient less had attained vision of 20/30 with surgical treatment, columns 7 and 10 would have

been almost identical. Therefore, it seems that the results following sinal surgery are not appreciably better than those following other types of therapy.

D. Final Visions in 65 Eyes: In column 11 are given the final visions of the total of 65 eyes which have just been discussed. Of these eyes, 12 were seen only once, within a month of the onset; 25 were seen once, from thirty-five days to twenty-eight years after the attack, and the other 28 were followed after treatment.

Forty-one eyes (63.1 per cent) had vision of from total blindness to 20/100. Fourteen eyes (21.5 per cent) had vision of from 20/30 to 20/20. Twenty-three eyes (35.4 per cent) had atrophy of the optic nerve, and 20 of these eyes had vision of 20/200 or less. In 10 eyes (15.4 per cent) the condition was unchanged or became worse during treatment.

The average duration of loss of sight prior to treatment for 12 of the improved eyes was eleven days per eye, and the average time of improvement for 14 of the improved eyes was thirty-four and three-tenths days per eye (table 1, column 5). Three other eyes required one hundred and eighty-four, three hundred and thirty, and five hundred and seventy days to attain their best final vision. If these eyes are included, the average time of improvement for 17 eyes is ninety-two days per eye.

It may be said, from a consideration of table 1, that sinal operation is better than no treatment but that removal of foci of infection is no better than nonsurgical therapy, that with the therapeutic agents in general use the results are not very good and that in cases of acute retrobulbar neuritis there is no marked "natural" tendency for the condition to improve spontaneously.

II. PATIENTS TREATED ONLY WITH VASODILATORS

During the past eight years, 23 patients who had 27 attacks of acute retrobulbar neuritis involving 29 eyes have been treated with only vasodilators.[30] The most essential data for these cases are outlined in table 2.

30. In eighteen attacks, intravenous injections of sodium nitrite (0.1 Gm.) were given. The average treatment was eight daily injections. One patient received only four daily injections, and 1 received eighteen daily injections. One patient received injections twice daily, and 1 received ten injections in eighteen days.

In 4 attacks, intramuscular injections of acetylcholine (0.1 Gm.) were used. In 3 instances, daily injections were given for five, six and nine days. The other patient received three injections in ten days.

In 1 attack, three daily inhalations of amyl nitrite was the only therapy used.

In 2 attacks (cases 4 and 25) injections of sodium nitrite and inhalations of amyl nitrite at home were used.

In 2 attacks (cases 17 and 23) intravenous injections of sodium nitrite and one or two retrobulbar injections of acetylcholine were given.

Fields were taken in all cases. They contributed to the diagnosis and were of assistance in ruling out tumors of the brain. Since this paper is concerned primarily with the pathologic physiology and therapy of acute retrobulbar neuritis, the field changes and their interpretation have not been included in this presentation.

A few other patients have been treated successfully with vasodilators, but reports of them have not been included in this study because they received some other therapy (such as sinal operation or injections of foreign protein) just prior to or simultaneously with the use of vasodilators. However, 1 case (case 9) is included in which an attack developed while the patient was receiving intranasal therapy for acute frontal sinusitis; in another case (case 21) an abscessed tooth had been removed thirty days before I saw the patient, with no resulting improvement in vision, and in case 7 a tonsillectomy had been performed fifty-three days before I saw him, with questionable improvement in vision.

Six of the attacks occurred in 3 patients who had multiple sclerosis. The incidence of multiple sclerosis is low because only patients with acute conditions are included in this study and neurologic examinations were not done in 12 of the patients. However, since the presence of multiple sclerosis is not a contraindication to vasodilator therapy, since the patients with multiple sclerosis responded well to this therapy (2 eyes attained vision of 20/20 and 4 eyes attained vision of 20/25) and since the neurologists have nothing specific to offer for the treatment of multiple sclerosis, it is my opinion that a neurologic examination, though it completes the work-up, offers nothing which will aid in therapeusis. Also, if multiple sclerosis is found, the usual tendency is for the ophthalmologist to shift the responsibility of the case to the neurologist.

Only 4 patients were hospitalized. Patient 9, a nurse, was taken off duty for seven days; patient 15, a child of 13, was hospitalized for ten days because she lived a great distance from the clinic; patient 16 was hospitalized for eight days because she could not be induced to return to the clinic daily, and patient 25, a very uncooperative patient, was hospitalized in another hospital for five days after she had left my service. So, a total of thirty hospital days, most of which were unnecessary, were used. If each patient had been hospitalized until "cured," approximately two hundred and sixty-five hospital days would have been required. The saving of time, money and hospital beds is obvious.

It is impossible to tell how many operations on the nasal sinuses were averted. This therapy had been advised for several of the patients referred to me. In the cases of patients seen first by me examination of the sinuses was not made until after vasodilator therapy had been

TABLE 2.—*Data for Twenty-Nine Eyes Treated Only with Vasodilators*

Attack	Patient	Age	Sex	Date of Onset	Duration of Visual Loss Before Therapy Was Started, Days	Eye	Vision	Fundus	Treatment [30]	Final Vision	Attained in, Days	Additional Data	Exposure to Cold or Climatic Change	Neurologic Data
1*	M. M.	31	M	February 1931	60	R	5/200	Temporal pallor, nasal blurring of disk; small hemorrhage in each fundus	Sodium nitrite, 6 daily injections	12/200	5	Pityriasis rosea; moderate drinker and smoker	+	Negative
						L	5/200	.....	.....	12/200	5			
2*	R. K.	29	M	June 13, 1932	18	L	3/200	Temporal atrophy of the optic nerve	Sodium nitrite, 6 daily injections	20/ 25	5	Uses 10 to 12 cigars daily	..	Multiple sclerosis 2 years
3*	R. K.	29	..	July 18, 1932	2	L	20/ 70—	Temporal atrophy of the optic nerve	Amyl nitrite, 3 daily inhalations	20/ 25—	2	.....	..	.....
4*	R. K.	32	..	Oct. 26, 1935	5	R	20/200	Normal	Sodium nitrite and amyl nitrite, 5 of each in 8 days	20/ 20—	9	Increased use of tobacco for 2 months	..	.....
5	R. K.	33	..	Aug. 17, 1936	8	L	20/200	.....	Sodium nitrite, 10 injections in 18 days	20/ 25	20	In April 1939, R and L = 20/20	..	.....
6*	M. O.	30	F	Nov. 25, 1933	6	R	20/ 50—	Disk blurred, veins engorged	Sodium nitrite, 6 daily injections	20/ 20—	6	.....	+	Negative
7†	C. P.	31	M	November 1933	60	R	20/ 40	Disk blurred nasally, veins engorged	Acetylcholine, 3 injections in 10 days	20/ 20—	10	Later had operation on sphenoid sinus	+	Negative
8*	E. T.	49	M	Feb. 7, 1934	14	L	20/ 30—	Normal	Sodium nitrite, 6 daily injections	20/ 25—	10	B. P. = 165/100	+	Refused
9*	N. P.	26	F	Feb. 4, 1935	4	R	20/ 50	Inferior veins engorged	Sodium nitrite, 7 injections in 6 days	20/ 20—	5	Right frontal sinusitis	+	Negative
10†	R. C.	21	F	Nov. 28, 1935	4	L	8/200	Disk blurred, veins engorged	Acetylcholine, 5 daily injections	20/ 25+	4	Lactating 3 months; head cold on day of attack	+	Refused
11	I. G.	40	F	May 4, 1936	10	R	20/ 70	Normal	Sodium nitrite, 7 daily injections	20/ 20—	6	Adenoma of thyroid; B. M. normal	..	Negative
12	B. D.	32	M	July 1936	90	L	20/ 50—	Veins engorged	Acetylcholine, 9 daily injections	20/ 30	9	Left vision always poorer than right	..	.....
13	F. D.	64	M	Dec. 23, 1936	18	R	20/100—	Normal	Acetylcholine, 6 daily injections	20/ 30—	5	Heavy smoker	+	.....
14	M. C.	52	F	Nov. 11, 1937	4	R	6/200	Veins engorged	Sodium nitrite, 8 daily injections	20/ 20	11	Head cold 10 days before attack	+	.....
15‡	G. G.	13	F	Dec. 13, 1937	9	L	8/200	Closure of superior retinal arteries; two separate field defects	Sodium nitrite, 10 daily injections	20/ 20	9	Retinal vessel closure and defect in lower field disappeared on the fifth day of treatment	+	Negative

								arteries; two separate field defects				and defect in lower field disappeared on the fifth day of treatment		
16	G. R.	26	F	Jan. 8, 1938	37	R	20/ 30	Temporal pallor of disk	Sodium nitrite, 6 injections in 4 days	20/ 20	4	Head cold 5 weeks before attack; menstruation began on day after attack	+	Multiple stenosis 3 years previous
17	J. S.	75	F	March 4, 1938	½ (7 hours)	R	3/200	Fundus picture resembles a thrombosis of the central retinal veins; papilledema of 1 D	Sodium nitrite, 10 daily injections; acetylcholine, 1 retrobulbar injection	20/ 20	26	.....	+	.....
18	S. B.	19	F	March 21, 1938	4	L	2/200	Papilledema of 3 D.; scotoma, 70 degrees in diameter	Sodium nitrite, 15 daily injections	6/200	14	Disk nearly flat and scotoma only 15 degrees in diameter on 14th day; head cold on day of attack	+	.....
19‡	M. P.	19	F	April 9, 1938	13	R	20/200	Temporal pallor of disk	Sodium nitrite, 18 daily injections	20/ 25	17	Lost position on April 8; April 9 a cold, wet day; previous attack February 1935	++	Multiple sclerosis
20	N. M.	26	F	May 11, 1938	7	L	20/200	Papilledema of 3½ D.	Sodium nitrite, 7 daily injections	20/ 20	7	Attack occurred on day menstruation was due; head cold 10 days earlier	..	.....
21	E. G.	33	M	May 26, 1938	32	R	20/ 50	Normal	Sodium nitrite, 3 daily injections	20/ 20	2	Heavy smoker	+	.....
22	E. G.	..	..	Oct. 11, 1938	6	R	20/ 40—	Normal	Sodium nitrite, 5 daily injections	20/ 25	4	Two weeks later, V = 20/20; in June 1939 had a right central angiospastic retinitis	..	.....
23	J. O.	28	F	May 30, 1938	2	L	10/200	Disk blurred, retina hazy	Sodium nitrite, 24 in 31 days; acetylcholine, 2 retrobulbar	20/ 20	45	Described fully in text	+++	.....
24‡	H. R.	28	F	May 30, 1938	1	L	H. M.	Papilledema of 3 D.	Sodium nitrite, 10 injections in 9 days	20/ 20	6	Disk flat and vision 20/40 after 3 days; head cold 2 weeks prior to attack	++	Negative
25	M. W.	23	F	Feb. 23, 1939	1	R L	4/200 H. M.	Normal	Sodium nitrite, 2 intramuscular injections, and 3 inhalations of amyl nitrite	20/ 20 4/200	11 11	Menstruation began on day of attack; case described in text	++++	Negative
26	D. K.	30	M	Aug. 2, 1939	37	R	20/ 30—	Normal	Sodium nitrite, 4 daily injections	20/ 15	3	Exposed to cold wind on motorcycle	++	.....
27	A. W.	32	M	Aug. 16, 1939	5	R	20/ 50	Lower half of disk elevated 2 D.; edema extends to macula	Sodium nitrite, 10 daily injections	20/ 30	7	Disk flat in 15 days; partial star-figure developed in macula while condition was improving	+++	.....

* Previously reported in Duggan.[9]
† Previously reported in Duggan, W. F.: Acetylcholine in the Treatment of Acute Retrobulbar Neuritis, Arch. Ophth. **17**: 579 (April) 1937.
‡ Previously reported in Duggan, W. F.: Tangent Screen Scotometry, Arch. Ophth. **23**: 316 (Feb.) 1940.

completed, in order to prevent any reflex or other effects, nonspecific in action, which might have influenced the final results.

The cases are listed in table 2 in the order of the dates of onset of the attacks because of a possible relation between climatic conditions and the attacks. However, for patients who had more than one attack (R.K. and E.G.) the attacks are grouped together. Average ages are calculated only from the first attacks.

In 19 patients 1 eye was involved once; in 2 both eyes were involved simultaneously; in 1 patient 1 eye was involved twice, and in 1 patient 1 eye was involved three times and the other eye once. Nine (39 per cent) of the patients were Jewish and 5 (22 per cent) were of Anglo-American stock. Other races included Irish, 3; Italian, 2; Negro, 2, and Polish and Spanish 1 each. Since most of the 71 patients analyzed in tables 1 and 2 came from in or near New York, this fact accounts in part for the preponderance of Jewish patients,

TABLE 3.—*Final Visual Acuity in Eyes Seen During the First Week of Attack and in Those Seen Later*

	Vision					Average Time of Improvement
	Less Than 20/200	20/30	20/25	20/20	20/15	
Fifteen eyes seen from 7 hours to 7 days after onset	2 (13.3%)	1 (6.7%)	3 (20 %)	9 (60 %)	.....	11 days per eye (13 eyes)
Fourteen eyes seen from 8 to 90 days after onset	2 (14.3%)	2 (14.3%)	4 (28.6%)	5 (35.7%)	1 (7.1%)	8.3 days per eye (12 eyes)

but a hypersensitive vascular system, peculiar to this race, also deserves consideration as a partial explanation of the racial incidence of acute retrobulbar neuritis.

Sex and Age.—There were 9 males. Their ages ranged between 29 and 54 years, and the average age was 36.8 years. There were 14 females. Their ages ranged between 13 and 75 years, and the average age was 30.4 years. Seven males were between 29 and 33 and 10 females were between 19 and 30 at the time of their first attack.

A rearrangement of the cases in the order of age or degree of visual loss did not permit any worth while conclusions to be drawn. However, when they were grouped according to the duration of visual loss prior to the beginning of therapy it was apparent that the final visual results were better in the cases in which treatment was given early (table 3).

Thus, for 15 eyes seen during the first week after the attack, before treatment, 10 (66.7 per cent) had vision of from perception of hand movements to 20/200, and after treatment, 12 (80 per cent) had vision of 20/25 or 20/20. And for 14 eyes seen from eight to ninety days after the attack, before treatment, 7 (50 per cent) had vision of from

perception of hand movements to 20/100, and after treatment, 10 (71.4 per cent) had vision of 20/25, 20/20 or 20/15.

In the patients seen early, the vision was, on the whole, poorer before treatment and better after treatment than in the patients seen later. The slightly more rapid improvement in the patients seen later is probably due to the fact that some of the perivascular edema in the optic nerve had been absorbed prior to treatment, while the fact that the visual results were not as good in the group seen later is undoubtedly due to the fact that some nerve fibers had been destroyed because of the prolonged anoxia.

Elimination of the Factor of Spontaneous Improvement.—For the 13 improved eyes which were seen from seven hours to seven days after the onset and treated, the average total time from the onset of the attack to the attainment of the best final vision was fourteen and six-tenths days (and the median time was twelve days). Only 3 of

TABLE 4.—*Visual Acuity Before and After Treatment in Eyes Seen From Thirteen to Ninety Days After the Onset of the Attack*

	Visual Acuity									
	3/200 to 5/200	Less Than 20/200	20/200	20/100	20/50	20/40	20/30	20/25	20/20	20/15
Before treatment.....	4	..	1	..	2	1	3	..	..	..
After treatment.....	..	2	..	..	..	..	2	3	3	1

these eyes had a total time longer than fourteen days. If these 13 eyes improved spontaneously and vasodilator therapy played no part in the recovery, then one would be justified in assuming that all patients seen after the thirteenth or fourteenth day should have shown approximately the same percentage distribution in visual acuities as is shown in the top row of table 3, in which 80 per cent of the eyes attained vision of 20/25 or 20/20.

Eleven eyes were seen from thirteen to ninety days after the onset of the attack (average time was 40 days per eye). In table 4 are assembled the visions before and after treatment for these 11 eyes.

It is apparent that before treatment 5 eyes (45.4 per cent) had vision of from 5/200 to 20/200, 3 eyes (27.3 per cent) had vision of 20/30 and in no case was vision better than 20/30. There is no hint of parallelism between these cases before treatment and the cases listed in the top row of table 3, in which 80 per cent of the eyes had 20/30 or better (mostly better) vision in an average total time of fourteen and six-tenths days per eye.

Moreover, 9 (81.8 per cent) of the 11 eyes listed in table 4 attained vision of from 20/30 to 20/15 in an average time of seven and

two-tenths days per eye after vasodilator therapy was instituted. In other words, the final visual results were almost as good as in the 15 eyes treated during the first week of the attack, and the average time of improvement was somewhat shorter because there had undoubtedly been some subsiding of the acute lesion. However, as is apparent from the cases listed in table 1, this tendency toward absorption of the edema cannot be depended on to effect a cure.

Visual Results.—In table 5 are summarized the visual findings before and after therapy for the 29 eyes treated only with vasodilators. Before treatment 17 eyes (58.6 per cent) had vision ranging between perception of hand movements and 20/100. After treatment 25 eyes (86.2 per cent) had vision ranging between 20/30 and 20/15.

TABLE 5.—*Visual Acuity for Twenty-Nine Eyes Before and After Vasodilator Therapy*

	Vision After Treatment					
Vision Before Treatment	Less Than 20/200	20/30	20/25	20/20	20/15	Totals Before Treatment
Hand movements to 5/200	4	..	1	3	..	8 (27.6%)
6/200-10/200	..	..	1	3	..	4 (13.8%)
20/200	..	..	2	2	..	4 (13.8%)
20/100	..	1	..	..	..	1 (3.5%)
20/ 70	..	..	1	1	..	2 (6.9%)
20/ 50	..	2	..	3	..	5 (17.2%)
20/ 40	..	..	1	1	..	2 (6.9%)
20/ 30	..	..	1	1	1	3 (10.3%)
Totals after treatment	4(13.8%)	3(10.3%)	7(24.1%)	14(48.3%)	1(3.5%)	

For the 25 improved eyes the average duration of loss of sight prior to therapy was sixteen days and the average time required for the attainment of the best final vision was nine and seven-tenths days per eye. (The median value for the duration of loss of sight prior to treatment and the time required for cure after the institution of treatment was seven days in each instance.)

In no instance did the vision become worse during treatment. However, 4 eyes did not attain vision of even 20/200. Two of these eyes were not seen until sixty days after the onset, and 1 eye was under observation for only eleven days (during which time the vision of the patient's other eye improved to 20/20). The remaining eye was observed for fourteen days, during which time the scotoma decreased in size and papilledema of 3 D. disappeared; two years later the patient had vision of 20/30.

Atrophy of the Optic Nerve.—Among the 26 eyes primarily involved, temporal pallor or temporal atrophy of the optic nerve was present in 5 eyes when they came under observation (patients with attacks 1, 2, 16 and 19). No improvement in the appearance of the disk resulted

from the treatment, although vision improved to 20/25 or 20/20 in patients with attacks 2, 16 and 19. Multiple sclerosis was present in these 3 cases.

Of the treated patients, in only 1 (attack 6) a small area of pallor developed at the lower pole of the disk. As this patient had a permanent scotoma, with vision of 20/20, it is likely that a thrombosis of one small vessel in the optic nerve accounted for the development of the pallor. It is possible that atrophy of the optic nerve developed during attack 18 and in the left eye of the patient with attack 25.

Therefore, the incidence of atrophy of the optic nerve following vasodilator therapy was not greater than 10 per cent, and it was minimal in 1 of these cases and not certain in the other 2 cases.

Papilledema.—The presence of papilledema of from 1 to 4 D. was not an unfavorable prognostic sign in 4 patients.

In the patient with attack 17 there was papilledema of 1 D. The vision was 3/200; there was a large central scotoma, and there were so many retinal hemorrhages that the fundus picture was that of thrombosis of the central retinal vein. On the seventh day of treatment, the vision was 20/40–, the disk was flat and no scotoma could be definitely elicited. One could say that the retrobulbar neuritis was over at this time. With slow absorption of the retinal hemorrhages, vision improved to 20/20 on the twenty-sixth day.

In the patient with attack 18 the vision was 2/200, with papilledema of 3 D. and a central scotoma 70 degrees in diameter, when the patient was first seen. On the fourteenth day of treatment, the disk was practically flat (less than 0.5 D. of swelling), the scotoma was about 20 degrees in diameter and the vision was 6/200. The patient failed to return for further observation. I was informed that the patient's vision in March 1940 was 20/30.

In the patient with attack 20 the vision was 20/200 and there was papilledema of nearly 4 D. After seven days of treatment, the vision was 20/20, the disk was normal and there was only a tiny paracentral scotoma, 3 degrees in diameter, for a 1/1,000 white stimulus.

In the patient with attack 24 the vision was limited to perception of hand movements in the extreme periphery of the field, and there was papilledema of 3 D. After three days of treatment the disk was flat and the vision was 20/70. The next day the vision was 20/40—, and on the sixth day it was 20/20 and there was only a small scotoma in the nasal field.

Patients with attacks 18, 20 and 24 were studied with the permission of Dr. Hobart Agnew.

Multiple Sclerosis.—Six of the attacks occurred in 3 patients who had multiple sclerosis. Neurologic examinations gave normal results in 8 other patients; permission for the examination was refused by 2

patients, and 10 others were not examined. In my opinion the only fundamental difference between acute retrobulbar neuritis and multiple sclerosis is in the location and extent of the lesions, and the same is true of acute retrobulbar neuritis and neuromyelitis optica. When the lesion is limited to the optic nerves or chiasm the condition may be called monosymptomatic multiple sclerosis (Traquair) or monosymptomatic neuromyelitis optica. The differences are quantitative, not qualitative.

In multiple sclerosis the glial scar does not just develop and compress the myelin sheaths and blood vessels; the sites of predilection for the lesions of multiple sclerosis are perivascular (Dawson), and this is also true of neuromyelitis optica, which is considered by some ophthalmologists to be acute multiple sclerosis. The myelin sheaths are more sensitive to lack of oxygen than the axones are, and just as connective tissue may develop in anoxic areas in other parts of the body, so does glial tissue (the connective tissue of the nervous system) proliferate in anoxic regions in the nervous system. The vascular lesion which causes localized anoxia is primary; the glial overgrowth is secondary. As early as 1913 Oppenheim stated in his textbook "Lehrbuch der Nervenkrankheiten" that multiple sclerosis could be caused by a "general vascular disease." Also, Kennedy [31] mentioned that "the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels." He stated the belief that the episodes, intermissions and curability of the acute crises of multiple sclerosis "resemble the happenings of localized allergic edemas."

Case 1.—The case of R. K. (attacks 2, 3, 4 and 5) demonstrates the value of vasodilator therapy in multiple sclerosis. His four attacks of retrobulbar neuritis involved the left eye three times and the right eye once. All attacks responded rapidly and favorably to vasodilator therapy. While he was under daily observation the vision improved to 20/25 after three attacks and 20/20 after the fourth. The eventual final vision, however, was 20/20 in each eye.

In addition, the symptoms and signs of multiple sclerosis always improved coincidentally with the improvement in vision. Among these symptoms were marked fatigability on exertion, loss of bladder control, paresthesias and disturbances in gait. At one time hyperphoria due to sudden paresis of a superior rectus muscle cleared up after treatment with intravenous administration of sodium nitrite, and at another time numbness of the outer half of the third finger and of the fourth and fifth fingers of one hand disappeared after three injections of sodium nitrite.

Worry and an increase in the consumption of tobacco seemed to be the principal factors which precipitated ocular and other symptoms in this patient's case.

He was observed from July 1932 to April 1939, at the end of which time the vision was 20/20 in each eye. He had not been hospitalized for multiple sclerosis during this period, and according to his neurologist, he was in better condition in

31. Kennedy, F.: New York State J. Med. **36**:469 (April 1) 1936.

December 1938 than at any previous time. Multiple sclerosis was first discovered in 1930, at which time he had been hospitalized for six weeks.

In 1934 Putnam [32] suggested that vascular abnormalities might be the etiologic basis of multiple sclerosis. In a later article [33] he reported that venular thrombi occurred during the encephalitis following tonsillitis, antirabic inoculations, vaccination, measles and grip and that the lesions were similar to those of multiple sclerosis. While Putnam emphasized venular thrombi as the primary pathologic change and while Simon and Solomon [34] reported that the blood of patients with multiple sclerosis shows an abnormally increased tendency to coagulate after injections of epinephrine and typhoid vaccine, I think that these changes are secondary and that the primary changes consist of arteriolar spasm and capillary dilatation, with increased capillary permeability and resulting anoxia of the tissue. This interpretation is of fundamental importance from the pathologic, clinical and therapeutic viewpoint. Moreover, since vasodilator therapy materially aids in the treatment of the acute retrobulbar neuritis of multiple sclerosis, it should be of value in the treatment of other manifestations of the disease, as in my patient, R. K., during seven years.

Two other patients also had multiple sclerosis. Both attacks were related to cold weather. Attack 16 occurred in patient G. R. on the day before menstruation. Attack 19 occurred in an excitable Italian girl who was discharged from her position the day before. The weather on the day of her attack was cold and wet.

Other Etiologic (?) Factors.—Head colds occurred seven to fourteen days before the attack in 4 cases and on the day before or the day of the attack in 2 cases. One patient had frontal sinusitis. One patient was a lactating woman, and another was a patient who also had pityriasis rosea.

Patient E. G. (attacks 21 and 22) had two mild attacks of acute retrobulbar neuritis in the right eye. Ten months after his second attack central angiospastic retinitis developed in the right eye, which also responded rapidly to vasodilator therapy.

In 3 cases menstruation began on the day of or the day after the attack (attacks 16, 20 and 25); in 2 cases menstruation seemed to be unrelated to the attack, and 2 of the patients had passed the menopause. So, in 25 per cent of 12 female patients between 13 and 40 years of

32. Putnam, T. J.: Science **80**:295 (Sept. 28) 1934.

33. Putnam, T. J.: Lesions of Encephalomyelitis and Multiple Sclerosis: Venous Thombosis as the Primary Alteration, J. A. M. A. **108**:1477 (May 1) 1937.

34. Simon, B., and Solomon, P.: Multiple Sclerosis, Arch. Neurol. & Psychiat. **34**:1286 (Dec.) 1935.

age there was at least a casual relation between the loss of sight and the onset of menstruation. This may or may not have been of significance, because in the 3 cases there was also a history of exposure to cold or chilling just prior to the attack of acute retrobulbar neuritis.

In most cases there were several suggestive etiologic factors; in a few cases there was apparently a single factor (usually exposure to cold or chilling), and in 2 attacks, 11 and 22, no likely etiologic factors could be elicited from the history or from the results of clinical and laboratory examinations.

The Relation of Changes in the Weather to the Onset of Acute Retrobulbar Neuritis.—Casual study of table 2 would indicate that such factors as lactation, head colds and multiple sclerosis were of etiologic importance in this condition.

In March 1938, when I saw patient J. S. (attack 17), I became interested in the relation of sudden climatic changes to the onset of acute retrobulbar neuritis. The general aspects of this relation between weather and disease have been discussed by Petersen in his monumental work "The Patient and the Weather."

Among the patients with the last 11 attacks (17 to 27), 9 gave a definite history of exposure to cold or of being exposed to a sudden change in climatic conditions. The change was usually either from warm to cold weather or from a cold dry to a cold wet atmosphere. Such a history was often elicited from patients in whom the condition occurred during the warmer months of the year. May 1938 was a relatively cold month; May 28 was stormy, and May 29 was very cold. Four attacks were observed during this particular month, and 3 of them occurred between May 26 and May 30. One patient (attack 23), a Negress aged 28, attended a "swing" session on Riker's Island on May 29. She apparently indulged in periods of extreme muscular activity and emotional exaltation and then sat down and rested in the chilly air. When she awoke on May 30 her left eye was nearly blind. The condition in this case was the worst in the series. In addition to a huge scotoma, there was blurring of the disk and the retina was hazy and edematous, so that at one time some surgeons in the clinic thought that she had a shallow detachment of the retina. However, with the intravenous administration of sodium nitrite, the fundus cleared, the disk became normal, the scotoma disappeared and the patient attained normal vision in forty-six days. The factors of exercise, perspiration, rest and chilling, plus the possibility of mild alkalosis due to blowing off of carbon dioxide (which would raise the dissociation curve of oxyhemoglobin), all probably played some part in precipitating the attack. In addition, she had a head cold during the week preceding the attack.

Attack 26 occurred in August. The patient drove a motorcycle and his face was exposed to the cooling effect of the air.

The patient with attack 27, who also had an attack in August, had been swimming in cold water three days before his attack, and on the night before the attack he had slept near an open window without any covering.

The patient with attack 25, studied with the permission of Dr. E. Lyon, is the most interesting in the series because exposure to cold seemed to be the only etiologic factor of importance. Later it was discovered that her diet was inadequate and that she smoked excessively.

CASE 2.—M. W., an unmarried woman aged 23, had two minutes of ultraviolet therapy on Feb. 22, 1939, the coldest day of the year in New York and vicinity. Later in the day she walked against a stiff cold wind for one hour. On awakening on February 23 she noticed that the vision in the left eye was markedly reduced; that afternoon vision in the right eye began to fail. Menstruation started on this date. About 11 p. m. she was seen by Dr. Lyon, who found that her vision was reduced to 4/200 in the right eye and to perception of hand movements in the left eye. The fields were contracted and the fundi were normal.

When I saw the patient on February 24 there was no change in these findings. In addition, the skin of the extremities felt cold and had a marble-like appearance, and there were no superficial veins anywhere on the body. The patient stated that she had always suffered from cold hands and feet, and a relative informed me that the patient "lived on cigarets and coffee and did not eat anything." Hence, nicotine and a multiple vitamin deficiency may have been contributory factors.

The patient was given 100 mg. of sodium nitrite intramuscularly and amyl nitrite by inhalation. After twenty minutes the vision was 10/200 in the right and 2/200 in the left eye. She inhaled amyl nitrite twice at home and was given another injection of sodium nitrite on February 25, at which time the visual acuity was unchanged but the fields were less contracted and the patient said that she could see better. She failed to return, and I next learned that she had entered the Hospital for Joint Diseases, where a neurologic examination gave negative results. She left the hospital on March 2, with vision of 20/40 in the right eye. On March 7 the vision was 20/20 in the right and 4/200 in the left eye; the right field was normal, and the left was still contracted.

In spite of her poor cooperation I think that the two injections of sodium nitrite and the three inhalations of amyl nitrite contributed to the improvement in the right eye.

This case is similar in some respects to a case reported by Horton, Brown and Roth.[35] One of their patients collapsed and was unconscious for forty minutes after running four blocks against a stiff wind at a temperature of 30 F. below zero. He did not recover his strength for a week. While these authors do not make any diagnosis other than that of hypersensitivity to cold, yet the condition resembles mild myelitis. Bilateral retrobulbar neuritis developed in my patient under the same circumstances. Had both conditions developed in either patient, the diagnosis of neuromyelitis optica could have been made. In other words, the distribution of lesions and the size of lesions determine the

35. Horton, B.; Brown, G., and Roth, G.: Hypersensitiveness to Cold, J. A. M. A. **107**:1263 (Oct. 17) 1936.

diagnosis of myelitis, retrobulbar neuritis and neuromyelitis optica. The differences are quantitative, not qualitative.

Horton, Brown and Roth ascribed the symptoms in their case to histamine, produced in the skin by the action of cold and then carried by the blood to the rest of the body, where, according to Topley,[36] it would act on histamine-sensitive cells (capillary endothelium, smooth muscle and gland cells). In my opinion histamine or a histamine-colloid compound was a direct or contributory cause of the acute retrobulbar neuritis in the case just described and in all cases in which a sudden change in the weather is closely associated with the onset of symptoms.

In the cases in table 2, 19 of the 27 attacks occurred either in the winter months or in the summer months with a history of exposure to cold or drafts, bathing in cold water or almost coincidentally with a sudden change in the weather.

COMMENT

The essential pathologic changes of acute retrobulbar neuritis are arteriolar spasm and increased capillary dilatation and permeability with transudation of plasma and lymphocytes, usually in a single arteriolar-capillary unit in the optic nerve or chiasm. The transudation of plasma causes localized edema, which when located in the optic nerve, and because of the thick sheath of the optic nerve, may increase the pressure within the nerve to such an extent that all the nerve fibers are unable to function normally. The result is acute anoxia of the tissue.

In the stage of physiologic abnormality, acute and temporary loss of function of a variable number of nerve fibers is the immediate result. It must be emphasized that the arteriolar and capillary changes are due to an exaggeration of the normal arteriolar and capillary reactions which occur in health. This viewpoint was concisely stated by Horder,[37] who recently stated that disease is a morbid physiologic state and that the functions by which a man lives in health are the same as those through which he expresses his pathologic state. If the anoxia is prolonged, pathologic changes become permanently fixed, as evidenced by atrophy of the optic nerve, demyelination of nerve fibers, glial proliferation, partially or completely obliterated arterioles and some permanent loss of function.

When the lesion is in the stage of pathologic physiology, early treatment directed toward the primary vascular changes can often effect a complete and rapid return of function to normal. If the function returns to normal, the early pathologic changes in the optic nerve (edema,

36. Topley, W. C.: An Outline of Immunity, Baltimore, William Wood & Company, 1933.

37. Horder: Brit. M. J. **1**:632 (March 25) 1939.

constricted arterioles and dilated, leaking capillaries) must have returned to normal. When permanent organic changes are present, vasodilator treatment obviously can have less effect, although even here nerve fibers which are on the borderline between life and death, living but not functioning normally, may recover if the blood supply is increased, thereby increasing the supply of available oxygen.

It must be ovious that the description of the acute pathologic picture of retrobulbar neuritis is a description of the acute pathologic picture of allergy and that one could say that all conditions of this kind are due to allergy. The cause may differ from case to case, but the basic arteriolar and capillary changes represent the final common pathway for a number of etiologic factors. This pathologic picture differs quantitatively from tissue to tissue and from organ to organ only because tissues and organs differ inter se. Therefore, one is forced to draw the conclusion that vasodilator therapy is the treatment of reason and choice for all acute allergic lesions. As early as 1914 Mautner and Pick,[38] in treating patients with anaphylactic shock, obtained good results from the vasodilator action of nitrites.

The specific pathologic changes of acute retrobulbar neuritis can result from a number of etiologic factors. A few of these are: endocrine imbalance which occurs at menstruation and during lactation; sympathetic overaction, as in the cases in which an emotional upset is a factor; insufficiency of acetylcholine or excessive destruction of acetylcholine, which may be linked to insufficiency of thiamine in the diet; avitaminosis of the B group in which, in addition to lack of thiamine, the nicotinic acid (which has a vasodilating action) intake is too low; histamine, which is the probable cause of the conditions occurring after the sudden onset of cold, wet weather; histamine-colloid compounds, which are formed as a result of the antigen-antibody reaction in conditions ascribed to allergy and focal infection; nicotine, which is known to cause vasoconstriction; loss of sodium chloride from the blood plasma in hot weather, leading to a change in the osmotic conditions in the blood; mild alkalosis due to the hyperpnea following exercise, whereby the oxyhemoglobin gives up its oxygen less readily; conditions causing anemic anoxemia, such as hemorrhage, carbon monoxide poisoning and methemoglobin formation due to sulfanilamide and related drugs, and finally substances which seem to act primarily on the capillary endothelium, such as venoms and various drugs.

In most cases of acute retrobulbar neuritis all examinations, both laboratory and clinical, give normal results. In other words, there is localized anoxia without anoxemia. The occasional occurrence of this

38. Mautner, H., and Pick, E. P., cited by Sollmann, T. H.: A Manual of Pharmacology, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 446.

condition in the presence of anoxemia means only that acute localized anoxia is superimposed on preexisting anoxemia.

In the final analysis, all causes can be reduced to one common cause: a localized lack of available oxygen. Excessive arteriolar constriction alone can cause capillary dilation and increased capillary permeability, which means that the capillaries do not receive enough oxygen-containing blood to function normally and that the tissues supplied by these capillaries also suffer from lack of oxygen. Substances which act only on the capillary wall, increasing the permeability, can also cause perivascular edema and tissue anoxia. Histamine, venoms and various drugs, as well as an insufficiency of ascorbic acid and a lack of oxygen (Landis), cause this condition. However, the eventual result of all etiologic agents mentioned in the last three paragraphs have one property in common: they cause tissue anoxia, and except for minor differences, the clinical picture is the same.

Histamine is the only substance which acts on both arterioles and capillaries; it constricts the arterioles and dilates and increases the permeability of the capillaries. It is produced in the skin by cold, heat and ultraviolet rays and in the intestines by the action of bacteria on the products of protein breakdown. In minimal amounts it probably plays an important role in regulating the permeability of capillaries, so Dale, Abel and others classed it with the hormones. It is less effective in the presence of oxygen. Best and McHenry [39] have shown that an enzyme, histaminase, seems to be important in the removal of histamine. However, this enzyme is most effective in the presence of oxygen; so the destruction of histamine is probably oxidative in nature. Also, histaminase is a tissue extract, and since many tissue extracts have vasodilating properties, it may be that such an action plays a part in the neutralization of histamine by histaminase in vivo.

Histamine-colloid compounds apparently play a major role in the development of lesions due to anaphylaxis, allergy and focal infection. The histamine portion of the compound accounts for the smooth muscle and capillary phenomena, while the colloid portion of the compound accounts for the specific antibody reactions and possibly for the specific organ or tissue localization of the different allergic reactions. According to Topley,[36] the most dramatic features of anaphylactic shock are the result not of the antigen-antibody reaction itself but of the liberation of histamine by the injured cells and the secondary response of the histamine-sensitive cells throughout the body.

It is perhaps unfortunate that the bacteriologic approach to disease has dominated medicine for the last forty or fifty years. Most of the work on allergy has been concentrated on the antigenic reactions of the

39. Best, C. H., and McHenry, E. W.: Physiol. Rev. **11**:371 (Oct.) 1931.

body fluids. All sorts of bacterial products have been used in therapy. A complicated terminology has developed which the average physician cannot understand and which is of no possible aid in planning treatment. Little attention has been given to histamine, although for years one theory of allergy and anaphylaxis has been known as the "histamine theory." It has been known also for years that the toxic effects of histamine are partially neutralized by an adequate supply of oxygen, that its removal is oxidative and, more recently, that histaminase acts most effectively in the presence of oxygen. Yet it is only since the discovery of histaminase that treatment directed specifically toward the histamine reactions has come into limited use. Even in cases of such reactions the immunologic approach is popular, and patients who already have too much histamine are given a little more on the theory that it either desensitizes (?) or promotes the formation of histaminase.

A small amount of histamine probably aids the passage of fluid and oxygen to the tissues by slightly increasing the permeability of the capillary endothelium. The oxygen, in addition to supplying the tissue cells, either directly or indirectly destroys the histamine; the capillary permeability decreases, and resorption of fluid and waste products occurs. If there is an excessive amount of histamine present or an insufficient available supply of oxygen the condition changes from the zone of normal physiology into the zone of pathologic physiology and impaired function, in which there may be arteriolar constriction, the capillary permeability is increased abnormally, the capillaries become dilated and there is hemoconcentration in the capillaries and localized edema, first microscopic and then macroscopic. This is the picture of shock, an acute localized shock, as also described by Moon [29] for a simple urticarial wheal. At this stage if an abundant supply of oxygen can be made available to the tissues by dilating the arterioles, a complete return to normal physiology and normal function is possible. However, if the localized anoxia lasts too long (and "too long" may be only a few minutes for nerve cells or parenchymatous cells, while it may be hours, days or weeks for nerve fibers) or if a thrombosis occurs in the capillaries, a localized infarct results, with more or less permanent loss of function. For this reason early treatment is essential. Much valuable time can be wasted while awaiting the results of various examinations. Once a diagnosis is made, a complete work-up is valuable only as a source for statistics. It contributes little or nothing of value to the treatment of this condition.

It is not my intention to state that histamine is responsible in all cases of acute retrobulbar neuritis. Histamine or histamine-colloid compounds probably are the chief etiologic agents in the conditions, associated with, for example, sudden climatic changes, exposure to cold or head colds. All of the possible agents previously listed must be considered. The

arteriolar-capillary changes account for the condition in all cases, and except in the cases in which the condition occurs in the presence of anemic anoxemia, therapy should be directed toward these basic pathologic changes.

On clinical evidence one must assume, first, that in different persons different arteriolar-capillary units are hypersensitive to substances which can cause this localized picture of shock; second, that at different ages in all persons different arteriolar-capillary units are hypersensitive; third, that in persons with such hypersensitive arterioles and capillaries second attacks will be more frequent than first attacks in the general population, and, fourth, that patients who present such a hypersensitivity are likely to have hypersensitive arteriolar-capillary units in other parts of the body. With the application of these assumptions to acute retrobulbar neuritis, it is apparent that, first, if climatic, endocrine, dietary and other etiologic factors are really causative, not all persons exposed to these influences have acute retrobulbar neuritis; second, most of the patients are between the ages of 23 and 46; third, in the 71 patients listed in tables 1 and 2 there were 13 in whom both eyes were involved at approximately the same time and 9 who had eleven subsequent attacks in the same or opposite eye, indicating a definite hypersensitivity of the blood vessels in a definite type of tissue and a very high incidence of second attacks, and fourth, the presence of hypersensitive arteriolar-capillary units in other tissues than the optic nerve was demonstrated in 1 patient (attack 15) who also had spastic closure of the superior branch of the central retinal artery, in 1 patient (attack 21) who later had central angiospastic retinitis and in 2 patients with multiple sclerosis in whom multiple vascular lesions occurred throughout the white matter of the nervous system.

The relation of attacks of acute retrobulbar neuritis to a head cold can be explained on an allergic basis. There is usually an interval of from ten to fourteen days between the onset of the head cold and the retrobulbar neuritis, or the two may occur almost simultaneously. Animals require ten to fourteen days for anaphylaxis to develop, and this is the time which elapses before serum sickness develops in human beings. Presumably, in cases in which the condition develops from ten to fourteen days after the head cold a mild second infection may precipitate the allergic attack, while in cases in which the condition occurs with the onset of a head cold it may be assumed that there has been previous sensitization and such a head cold corresponds to the shocking dose of an antigen in sensitized animals.

However, the disease in all cases is not necessarily due to true allergy in which previous sensitization must be assumed. Since histamine mimics the action of allergy in man and of anaphylaxis in animals and since

no previous sensitization to histamine is necessary, conditions can occur in which the increased production or the decreased destruction of histamine is the causal factor. In other persons epinephrine may be the culprit; in still others, the condition may be due to a relative insufficiency of the vitamin B factors, and finally, endocrine imbalance, an all-inclusive term, may be the precipitating factor. This means that the hypothetical toxins which have been exploited as the cause of acute retrobulbar neuritis are not only endogenous in origin but are often the substances which are concerned with maintaining homeostasis within the organism. In most cases there are multiple causative factors at work, any one of which by itself would not produce the condition but in combination with one or more of the other factors is able to shift the reactions in the tissues from the zone of normal physiology to that of pathologic physiology. In a few cases an exogenous substance, such as nicotine or sulfanilamide, may act as a precipitating factor.

To sum up this discussion, it may be stated that acute retrobulbar neuritis is an acute vascular catastrophe in the optic nerve or chiasm which can have many causes. The immediate effect is acute localized tissue anoxia and loss of function.

The changes in the arterioles and capillaries are the final common pathway whereby different etiologic agents produce the same clinical and pathologic picture. Therapy directed toward these pathologic changes is both logical and effective.

CONTRIBUTORY EVIDENCE FROM THE LITERATURE

In 1913 Cross [40] stated that he though it possible that in some cases retro-ocular neuritis might be due to a spasm of small vessels going to the nerve fibers while in others it might be due to small emboli. In some it might be due to slight edema and in others to slight thrombosis.

Sourdille [41] in 1901 and Schieck [42] in 1909 suggested a primary vascular origin for acute retrobulbar neuritis, as did Aubaret and Sédan [43] in 1928.

In 1931 de Saint-Martin [44] reported a case of retrobulbar neuritis which occurred post partum and which improved with injections of acetylcholine. In 1934 Hartmann and Parfonry [45] reported a case of posthemorrhagic amblyopia, which improved with the administration of

40. Cross, R.: Tr. Ophth. Soc. U. Kingdom **33**:43, 1913.
41. Sourdille, C.: Clin. opht. **6**:280, 1900; abstracted, Arch. Ophth. **30**:191, 1901.
42. Schieck, F.: Arch. f. Ophth. **71**:466, 1909.
43. Aubaret, E., and Sédan, J.: Clin. opht. **32**:255, 1928.
44. de Saint-Martin: Ann. d'ocul. **168**:102 (Feb.) 1931.
45. Hartmann, E., and Parfonry, J.: Bull. Soc. d'opht. de Paris, February 1934, p. 56.

acetylcholine after repeated transfusions had been of no avail. They stated that a vascular spasm was the cause of the amaurosis.

In 1933 Snell [11] stated that real inflammation was not present in these cases and that the loss of sight could be attributed to stasis or edema.

In 1936 Kennedy,[31] in discussing allergic manifestations in the central nervous system, after mentioning the simultaneous occurrence of retrobulbar neuritis with eczema, urticaria and acute transient edema of the optic nerve, stated that he had observed in the same person "phenomena affecting other areas of the central nervous system—in the medulla, in the capsule, in the nerves of hearing, invisible to the eye but visible to the intelligence as being identical with those seen by the ophthalmoscope." And Bedell [46] said, in the same year, "Some cases of retrobulbar neuritis are allergic. The sudden edema of the optic nerve can and probably does cause the syndrome to which that name is applied."

Quantitative variations in the pathologic reactions of blood vessels, characterized by Ricker as "prestasis, peristasis and stasis or liquorstasis, leukostasis and rubrostasis," satisfactorily account for the pathologic physiologic and anatomic changes of acute retrobulbar neuritis. The immediate factor is acute localized tissue anoxia. As Moon [29] said: "If all agents which produce relaxation and permeability of capillaries shall be regarded as toxins, then the conception of toxemia is substantiated. However, that definition would include normal metabolites, cytoplasmic substances and lack of oxygen as toxins."

SUMMARY

I. The visual results in 65 eyes in which there had been an attack of acute retrobulbar neuritis and which were treated with therapy other than vasodilators have been analyzed.

1. In the treatment of 13 eyes, a surgical operation was performed on the nasal sinuses, with the following result: Six eyes (46.2 per cent) had final vision of from blindness to 20/100, and 5 eyes (38.4 per cent) had final vision of from 20/30 to 20/20.

2. Of 28 eyes which were treated by various means, including nasal operation in 8 cases, 17 eyes (60.7 per cent) were improved and 10 eyes (35.7 per cent) had a final vision of from 20/30 to 20/20. The average time of improvement for 14 of the 17 improved eyes was thirty-four and three-tenths days per eye. The other 3 improved eyes required one hundred and eighty-four, three hundred and thirty and five hundred and seventy days to attain their best final vision.

3. The visual results in the total 65 eyes were as follows: Forty-one eyes (63.1 per cent) had a final vision of from total blindness to 20/100;

46. Bedell, A.: New York State J. Med. **36**:959 (July 1) 1936.

14 eyes (21.5 per cent) had a final vision of from 20/30 to 20/20; 10 eyes (15.4 per cent) were unchanged or became worse with treatment, and 23 eyes (35.4 per cent) had atrophy of the optic nerve and 20 of these eyes had vision of 20/200 or less.

The impression was gained that there was no great natural tendency for these conditions to improve spontaneously and that nasal sinal surgery was nonspecific in its mode of action.

II. The visual results in 29 eyes in the treatment of which only vasodilator therapy was used were as follows: Before treatment 17 eyes (58.6 per cent) had vision ranging between perception of hand movements and 20/100; after treatment 25 eyes (86.2 per cent) had vision of from 20/30 to 20/15.

No conditions became worse with treatment, but in 4 eyes the final vision was less than 20/200. Two of these eyes were not seen until sixty days after the onset, so failure to obtain a better result cannot be attributed to the therapy. The other 2 patients did not continue attending the clinic, so therapy may be considered to have been inadequate and incomplete.

For the 25 improved eyes the average duration of loss of sight prior to treatment was sixteen days (median value, seven days) and the average time required for the attainment of their best final vision was nine and seven-tenths days (median value, seven days).

Papilledema and multiple sclerosis were not of unfavorable prognostic significance.

The earlier the treatment was begun, the better were the visual results. The lesson to be drawn from this is that after the diagnosis is made, valuable time should not be wasted searching for foci of infection and other questionable etiologic sources.

There is no necessity for operating on sinuses or other foci of infection unless such foci require surgical intervention because of the local condition in the foci, and not because of the presence of acute retrobulbar neuritis.

While intravenous administration of sodium nitrite, intramuscular administration of acetylcholine and inhalations of amyl nitrite are all of value, I personally think that intravenous administration of sodium nitrite is the most effective treatment because of the prolonged effect and because a high concentration of this drug in the blood is assured for a short time. Histaminase may be found to be of value as an adjuvant.

CONCLUSIONS

Acute retrobulbar neuritis is an acute vascular catastrophe occurring in the optic nerve, chiasm or tract which results in edema and leads to

tissue anoxia and loss of function. The pathologic picture is similar to that of shock and histamine poisoning.

The arteriolar-capillary changes are the final common pathway for a number of different etiologic agents all of which act primarily on the arterioles or the capillaries or both.

The onset in many cases seems to be related either to exposure to cold or to a sudden change in the weather. This relation is causal rather than casual. On clinical evidence histamine is probably the etiologic agent in cases of this type. The assumption must be made that certain cells are more sensitive than others to histamine, accounting for the sharply localized lesions.

Improvement in vision is more rapid and more marked when therapy is directed toward the arteriolar spasm than when other types of therapy are used or when no therapy is used.

The purpose of vasodilator therapy is to remove the arteriolar spasm, thereby facilitating the access of oxygen-containing blood to the tissues and eliminating the tissue anoxia.

The term acute retrobulbar neuritis is incorrect. Acute angiospastic neuropathy is a better term, as evidenced by the pathologic observations and therapeutic results. This classification includes conditions ascribed to allergy, focal infection, cold, lactation, avitaminosis and most of the other so-called etiologic agents.

Clinical Notes

BLOOD STAINING OF THE CORNEA DUE TO SUBCONJUNCTIVAL HEMORRHAGE

Report of a Case

LOUIS LEHRFELD, M.D., AND SOLOMON S. BRAV, M.D.,
PHILADELPHIA

Blood staining of the cornea, though a rather infrequent condition, is one which has been fairly well covered in the literature. The purpose of this communication is to report a case in which the etiologic factor was a large subconjunctival hemorrhage.

With notable exceptions, in all of the cases mentioned in the literature the condition has followed some trauma to the eye with resultant hyphema in the anterior chamber. This type of case was first mentioned by Baumgarten [1] in 1883, and reports by Lawford, Vossius, Weeks, Collins, Wells and Wadsworth and Verhœff followed.[2] Toulant and Morard [3] in France and Reese [4] and Larkin [5] in this country are the most recent contributors to this subject. Throughout their discussions there has been considerable theorization as to the nature of the pigment present and as to the means of entrance into the cornea. Collins claimed that the pigment was hematoidin, while Vossius stated that it was hemosiderin. Parsons [6] wrote that it might be caused by any of the hemoglobin derivatives, and to date this last theory is the accepted thought. There was likewise argument as to the mode of entry into the cornea. Roemer [7] and Vossius stated the belief that red blood corpuscles could be seen within the corneal interstices. However, the more recent views of Collins and of Duke-Elder [8] are that no such actual bleeding into the cornea occurs but rather that there is an adsorption of

From the clinic of Dr. Louis Lehrfeld, Wills Hospital.

1. Baumgarten, P.: Arch. f. Ophth. (pt. 2) **29**:117, 1883.

2. Lawford, J. B.: Tr. Ophth. Soc. U. Kingdom **8**:60, 1887-1888. Vossius, A.: Arch. f. Ophth. (pt. 2) **35**:207, 1889. Weeks, J.: New York Eye & Ear Infirm. Rep. **1**:37, 1893. Collins, E. T.: Tr. Ophth. Soc. U. Kingdom **15**:69-87, 1895. Wells, D. W.: Homeop. Eye, Ear & Throat J. **15**:497, 1909. Wadsworth, O. F., and Verhoeff, F. H.: Ophth. Rec. **14**:368, 1905.

3. Toulant, P., and Morard, G.: Arch. d'opht. **53**:241, 1936.

4. Reese, W. S.: Am. J. Ophth. **15**:1173, 1932.

5. Larkin, B. J.: J. Indiana M. A. **24**:365, 1931.

6. Parsons, J. H.: The Pathology of the Eye, New York, S. P. Putnam's Sons, 1908, vol. 1, p. 249.

7. Roemer, P.: Die Durchblutung der Hornhaut, Halle, C. Marhold, 1899.

8. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 2037.

pigment through Descemet's membrane and that this is made possible because of the prolonged contact of the blood with the posterior layer of endothelium.

Other causes of blood staining of the cornea have gone almost unnoticed in the literature. Pickard [9] reported that he had observed a case in which interstitial keratitis cleared with the usual antisyphilitic therapy, and Richter [10] commented on a child whom he once observed with universal cyanosis and ophthalmia neonatorum and with the cornea a bronze color. There is no mention of any other systemic disease which might cause this corneal change.

Thorough search of the literature has revealed no case report concerning blood staining of the cornea due to external sources, i. e., subconjunctival hemorrhage. Duke-Elder,[8] Parsons [6] and Lewis [11] mentioned that this condition is of rare occurrence and seen only when the hemorrhage is at or near the limbus. These authorities all agree that only the immediately adjacent area of the cornea is involved. Roemer [12] mentioned that the conjunctiva is firmly adherent at the limbus, so that it cannot be raised by subconjunctival blood unless there is a severe hemorrhage. Holloway [13] mentioned that this condition did occur and that the fact was not sufficiently well known to ophthalmologists. None of the aforementioned contributors gave any references to articles in the literature concerning this subject. We therefore desire to present the following case of blood staining of the cornea coincident with severe subconjunctival hemorrhage.

REPORT OF CASE

On May 10, 1940 H. H., a man aged 56, presented himself at Wills Hospital, service of one of us (L. L.), with a massive subconjunctival hemorrhage following a severe coughing spell. At that time the hemorrhage was of three days' duration. It was located from 6 to 10 o'clock, the entire sclera being covered up to the limbus. Vision in the right eye was 6/15 with -3.75 sph. Vision in the left eye was 6/9 with -0.50 sph. $\bigcirc$ -0.50 cyl., axis 10. On May 17 slit lamp examination by Dr. George Dublin revealed marked hemorrhage grossly. The cornea was clear, but the posterior layers near the limbus showed a green lemon tint. The remainder of the cornea showed no discoloration. The anterior chamber was normal, and there were no keratic precipitates noted. In addition, the patient happened to possess bilateral congenital remnants of pupillary membranes.

On May 29 there was still a faint yellow pigment line remaining between the pupil and the lower limbus. On June 21 no evidence of pigment and only slight evidence of the hemorrhage was to be seen.

---

9. Pickard, R., in discussion on Hudson, A. C.: Proc. Roy. Soc. Med. **26**: 606, 1933.

10. Richter, P. V.: Ophth. Klin. **8**:241, 1904.

11. Lewis, J. D.: Blood-Staining of the Cornea, in Wood, C. A.: The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1914, vol. 5, p. 3337.

12. Roemer, P.: Textbook of Ophthalmology in the Form of Clinical Lectures, translated by M. L. Foster, New York, Rebman Company, 1912-1913, p. 87.

13. Holloway, T., in discussion on Reese.[4]

COMMENT

Assuming Roemer to be correct in stating that the conjunctiva is so firmly adherent at the limbus that only severe hemorrhage will raise it, we may then presume that the pigment in this case was adsorbed directly into the substantia propria of the cornea and was thus seen in the interlamellar spaces. Why blood staining from this condition is not more frequent is somewhat difficult to explain except that most subconjunctival hemorrhages are neither sufficiently massive nor sufficiently near enough to the limbus to cause any conjunctival separation, minor though it may be, to allow for diffusion of the pigment. However, we believe that more frequent slit lamp examinations in search of this sequela of subconjunctival hemorrhage will probably reveal it to be present in many cases previously unobserved.

SUMMARY

A review of the literature on the subject of blood staining of the cornea is presented.

A case is reported in which subconjunctival hemorrhage was the etiologic factor.

A POCKET RULE FOR THE MEASUREMENT OF ACCOMMODATION AND OF CONVERGENCE

HENRY B. ABBOTT, M.D., BROOKLYN

The measurement of accommodation and of convergence should be a routine procedure in the ophthalmologic examination. Many instruments and methods have been devised for this purpose. In 1885 Landolt [1] described his dynamometer, an ingenious but rather awkward apparatus. Since then there have been many others, including the ergograph of Berens, Hardy and Pierce,[2] a refined apparatus for making graphic studies of the fatigue of these two functions. Most of my associates, however, use the Prince rule or a similar one. These rules, which are somewhat over 50 cm. long, always impressed me as being rather awkward to handle, and for some time I have thought about devising a small pocketable instrument.

The instrument [3] finally devised consists of a semirigid flexible steel tape which rolls up on a spring reel into a black metal case. The tape is stamped with centimeter graduations on one of its flat surfaces and

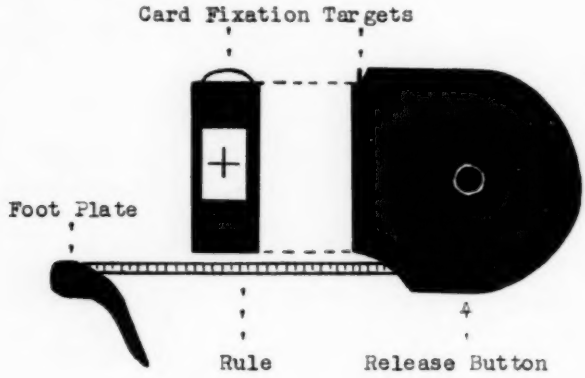
From the Long Island College of Medicine.

1. Landolt, E.: Arch. d'opht. **5**:97, 1885.

2. Berens, C.; Hardy, L. H., and Pierce, H. F.: Studies in Ocular Fatigue, in Contributions to Ophthalmic Science, Dedicated to Dr. Edward Jackson in Honor of His Seventieth Birthday, Menasha, Wis., George Banta Publishing Company, 1926, p. 102.

3. Manufactured by Clairmont and Nichols, New York.

dioptric or meter angle equivalents on the other. At its free end a plastic blunt foot plate to fit against the patient's face is attached. This contains a small trigger-shaped handle to be held between the ophthalmologist's thumb and index finger. The metal case has a release button for the spring reel which when pressed draws in the tape and when released stops the rule at the position desired. The case is constructed with a flat card-holding face perpendicular to the emerging rule. The card holder is made to hold two permanent white celluloid or renewable paper cards which are freely interchangeable and reversible, having different fixation figures printed on both sides of each card. The four figures are a black dot, measuring 2 mm., a small black engraved cross, an engraved Duane line and a line of closely spaced black dots. Each figure is centered on the card. The dot and the cross are used as fixation targets in testing convergence; the Duane line and the line of dots, for testing accommodation.



Lateral and front views of pocket rule.

The technic employed is similar to that of the various rules. The fixation card to be used is put in place. The foot plate of the instrument is then held against the patient's face, either below the orbital margin (accommodation test) or over the base of the nose (convergence test). The rule case with its fixation card is then withdrawn from the face until it is well beyond the range to be investigated. Then with fixation established, the release button on the case is pressed and the fixation target made to approach the face slowly until the limit of the test is reached. Pressure on the release button is then withdrawn, locking the rule at this position and allowing a leisurely or later reading.

This instrument is accurate and compact and when collapsed can readily be slipped into one's pocket or bag, where it will be available at all times. The small size and lightness of the rule make it adaptable to the measurement of interpupillary distances, while its additional length enables the checking of retinoscopic distances. The technic of its use is also considerably less awkward than with other methods commonly employed.

SOLUBILITY OF DRUGS IN BUFFER SOLUTIONS

JOHN G. BELLOWS, M.D., PH.D., AND HERMAN CHINN, PH.D.,
CHICAGO

In response to some inquiries received by this department concerning the use of homatropine and paredrine (4-hydroxy-α-phenyl-β-aminopropine; β-4-hydroxylphenylisopropylamine) at various p_H levels, we investigated their solubility and reaction in buffer solutions. Homatropine hydrobromide and paredrine hydrobromide [1] were employed in concentrations of 5 per cent and 2 per cent respectively. The buffer solutions were prepared according to Gifford.[2] All p_H determinations were made by means of a glass electrode.

In the p_H range investigated (4.20 to 8.75) the solutions remained perfectly clear after addition of the drugs. A slight alteration in the reaction of the buffer, varying from 0.05 to 0.35 p_H unit, was noted. The

Changes in Hydrogen Ion Concentration

p_H of Gifford's Buffer Solution	p_H Change After 5% Homatropine Hydrobromide 2% Paredrine Hydrobromide	p_H Change After 5% Homatropine Hydrobromide 2% Paredrine Hydrobromide + 0.04% Nipasol	p_H Change After 5% Homatropine Hydrobromide 2% Paredrine Hydrobromide + 0.5% Chlorbutanol	p_H Change After 5% Homatropine Hydrobromide 2% Paredrine Hydrobromide + 1% Chlorbutanol
4.60	+0.15	+0.15	+0.30	+0.50
6.50	−0.05	−0.10	−0.05	−0.05
7.15	−0.05	−0.15	−0.05	−0.05
7.45	−0.15	−0.10	−0.15	−0.05
8.05	−0.20	−0.20	−0.20	−0.20
8.75	−0.35	−0.35	−0.35	−0.35

greatest changes occurred in the more alkaline solutions. At p_H levels above 6.15 the shift was to the acid side, whereas at p_H 4.6 the solution became slightly more alkaline.

Buffer solution no. 1,[2] used as a collyrium, retains its clarity for long periods if a few simple precautions are taken. The stock solution should be kept on ice in a 4 ounce (120 cc.) bottle, from which ½ ounce (15 cc.) dropper bottle is filled as necessary. By this means contamination of the stock solution is minimized, and addition of a preservative is unnecessary. However, if a preservative is desired, it may be used without affecting appreciably either the clarity or the p_H of the solution. This can be seen from the accompanying table. The addition of 0.04 per cent nipasol (n-propyl-p-hydroxybenzoate) [3] had no effect on the reaction

From the Department of Ophthalmology and Chemistry, Northwestern University Medical School.

1. Supplied by Smith, Kline and French Laboratories.

2. Gifford, S. R.: Reaction of Buffer Solution and of Ophthalmic Drugs, Arch. Ophth. **13**:78-82 (Jan.) 1935.

3. Eschenbrenner, H.: Ueber Konservierung von Augentropfen mit dem Propylester der p-Oxybenzoesäure (Nipasol), Klin. Monatsbl. f. Augenh. **89**:238, 1932.

of the buffer. This preservative dissolved completely only above a p_H of 7.3. Chlorobutanol U. S. P. in concentrations of 0.5 per cent and 1 per cent likewise produced no change in the buffer solutions except at p_H 4.6. This preservative is not easily soluble. However, filtration or slight warming of the solution will overcome this difficulty.

Dr. S. R. Gifford has made helpful suggestions concerning this work.

A BETTER ADHESIVE TAPE FOR USE AFTER SURGICAL TREATMENT OF THE EYE

CLINTON WILSON, M.D., LOS ANGELES

It is well known that there is widespread allergy to ordinary adhesive tape, and occasionally a reaction may be so severe that its use is precluded for a certain patient.

Several years ago I was attracted by the possibilities inherent in Scotch tape as a substitute for adhesive tape treated with zinc oxide. At that time the adhesive qualities and the packaging of Scotch tape were not satisfactory, but it seemed from tests then carried on that the substance would be borne by the most sensitive skin.

Since these first tests much improvement has been made both in the adhesive qualities and in the packaging of Scotch tape, and it has come to be widely used in a number of clinics and by some physicians in private practice. Its use, however, seems not to be as widespread as would appear justified.

The convenience, cleanliness and ease of application and removal all combine to make this an ideal dressing for the eye after surgical therapy. It adheres well, even to slightly hairy surfaces, and can be painlessly removed by gentle pulling. Plain water will remove such adhesive substance as adheres to the skin. No dermatitic reactions have been seen at any time during the past two and one-half years in my practice, even in very sensitive skins which have reacted severely to adhesive tape treated with zinc oxide. Furthermore, it is convenient to the patient, because the tape can be inexpensively obtained at almost any stationer's.

USE OF BRILLIANT GREEN IN TREATMENT OF BLEPHARITIS

ANDREW G. FRANKS, M.D., NEW YORK

Following the suggestion of Tulipan,[1] I have treated 12 patients with nonulcerative blepharitis by applying brilliant green (tetraethyldiaminotriphenylmethane sulfate). Some of the lesions were associated with

1. Tulipan, L.: Brilliant Green for Treatment of Blepharitis, Arch. Dermat. & Syph. **33**:349 (Feb.) 1936.

seborrheic dermatitis, acne or sycosis vulgaris, and others were of unknown causation. The duration was from two weeks to four years.

The solution was applied to the eyelids daily for several weeks with a small applicator so as not to stain the surrounding skin unnecessarily. No ill effects were noted from getting any of the solution on the conjunctiva, but care was taken not to do so. During this time the patients wore smoked glasses to avoid attracting undesired attention. The stain wore off a few days after treatment was discontinued. Adult patients averred that there was a "tingling sensation," but children, the youngest of whom was 12 years old, stated that they felt no pain. No other treatment was used for the blepharitis, but the associated cutaneous diseases were given appropriate therapy.

The condition either cleared up entirely or greatly improved in all 12 patients. The last of these was examined a year before the writing of this report, and since then there has been no recurrence. This treatment has been gratifyingly effective for lesions refractory to other methods.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

PARALYSIS OF CONVERGENCE

KENNETH L. ROPER, M.D.
PHILADELPHIA

When the eyes are made to focus on a near object they are said to converge. Convergence results from a simultaneous and equal contraction of the two internal rectus muscles, producing equal movements inward, or convergence adduction, of the eyes. Adler [1] stated that this action is aided by simultaneous contraction of the superior and inferior recti and that during the act of convergence there is a wheel-like rotation of each eye around its anteroposterior axis, producing true extorsion. The upper pole of each vertical meridian rotates slightly outward, Spaeth [2] explained, because of the predominant effect of the inferior recti, which add extorsion to the accompaniment of rotation. This increases naturally as downward rotation increases.

To this active movement there may be added a passive phenomenon, inhibition of the external recti. Another phenomenon, that of accommodation, is associated with convergence. There exists between convergence and accommodation a close relation, so that normally the two cannot be separately demonstrated. With this intimate relation is a pupillary synergy, which is the constriction to convergence accommodation.

Thus, convergence is said to be absent, or paralyzed, when the patient cannot focus his visual axes on a more or less close object. Pure convergence paralysis is rare. Its occurrence in recent years has aroused interest because of its relative frequency following encephalitis and its parkinsonian complications. The condition has been observed in cases of multiple sclerosis and of certain tumors in the vicinity of the corpora quadrigemina. More frequently it is seen in association

From the Wills Hospital.

Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Master of Medical Science (M. Sc. [Med.]) for graduate work in ophthalmology.

1. Adler, F. H.: Clinical Physiology of the Eye, New York, The Macmillan Company, 1933, p. 273.

2. Spaeth, E. B.: Personal communication to the author.

with other paralyses, particularly that of accommodation. Its occurrence is often noted in conjugate movements of laterality and in cases of Parinaud's syndrome, in which it is found combined with paralysis of conjugate upward movement of the eye.

The first studies of disorders of convergence followed closely the early studies, in 1857, of Donders and Listing on the synergic movements of the eyes.[3] Parinaud [4] was probably the first to call attention to the condition. One of the cases cited in his article in 1883 was the basis for his famous syndrome. In it he observed paralysis of conjugate vertical movements and paralysis of convergence with preservation of lateral conjugate movements.[5] At the same time he reported a case of pure convergence paralysis with multiple sclerosis [6] and also described a case of paralysis of convergence associated with paralysis of accommodation; these conditions were later proved to be the early signs of a tumor in the region of the corpora quadrigemina.[7]

Parinaud's clinical observations, when coupled with his knowledge of the experimental researches of Duval, Laborde and Craux and the clinical observations of Prevost, Foville and Priestley Smith,[8] made him feel that the seat of the lesion in these cases was the cerebellum. Later on, when in cases reported by Wernicke and Henoch lesions were observed in one of the quadrigeminal bodies,[9] he thought that the center was in the tubercula quadrigemina.

Grandclément,[10] in 1894, described a case of convergence paralysis and stated the opinion that its occurrence during adolescence was of some significance. He believed there was a nucleus in the gray matter near the quadrigeminal bodies that produced the movement of convergence.

Straub,[11] in 1896, reported a case of this condition associated with third nerve palsy which slowly disappeared, leaving paresis of convergence with intact lateral movements. His case showed pupillary reaction, and he concluded that contraction of the pupil was associated

3. Donders and Listing, cited by Bussy.[36]

4. Parinaud, H.: Paralysie des mouvements associés des yeux, Arch. de neurol. **5**:145-172, 1883.

5. Parinaud,[4] observation no. 4, pp. 158-161.

6. Parinaud,[4] observation no. 7, pp. 165-166.

7. Parinaud,[4] observation no. 6, pp. 162-163.

8. Parinaud, H.: Paralysis of the Movement of Convergence of the Eyes, translated from the French by H. Juler, Brain **9**:330-341, 1887.

9. Parinaud,[8] pp. 340-341.

10. Grandclément: Paralysie essentielle et transitoire de la convergence, Lyon méd. **77**:401, 1894.

11. Straub, M.: A Case of Paralysis of Convergence with Remarks, Arch. Ophth. **25**:325-328, 1896.

with accommodation and not with convergence. He was convinced that the convergence paralysis was due to a lesion in the third nucleus. Kohler and Pick, he stated, had conclusively shown that the center for accommodation and pupillary reaction was not in but rather nearby the center for the internal recti.

Peters [12] stated the opinion that in 1 of his cases, reported in 1889, the condition resulted from trauma of the head. Hayne [13] reported a case of paralysis of convergence without impairment of associated movements but did not consider a history of slight trauma the causative factor.

Cestan [14] reported a case of convergence paralysis associated with paralysis of conjugate vertical movements. By referring to Spiller's case, in which a tumor in the middle of the peduncle and under the aqueduct of Sylvius was discovered, he came to the conclusion that the condition indicated a lesion of the upper part of the cerebral peduncles.

Pasetti,[15] in reporting 2 cases in 1913, formulated the conclusion that there is a center of convergence in man which is located outside the nuclei of origin of the motor nerves and the association center for pupillary movements.

Farnarier,[16] in 1913, reported a case in which the condition followed diphtheria and did not clear up in spite of intensive treatment.

Bollack,[17] reporting on ocular manifestations in a series of 20 cases of lethargic encephalitis, observed 2 cases of pure convergence paralysis and 5 cases in which the condition was associated with some other paralysis. In 4 of 7 additional cases Morax and Bollack [18] noted convergence paralysis in association with other paralyses.

Zentmayer [19] stated that Ellett, in discussion, mentioned 2 cases in which convergence paralysis was due to lethargic encephalitis.

---

12. Peters, A.: Ueber Convergenzlähmungen, Centralbl. f. prakt. Augenh. **13**:225-229, 1889.

13. Hayne, H. W.: Report of a Case of Paralysis of Convergence Without Impairment of Associated Movements, Arch. Ophth. **25**:328-332, 1896.

14. Cestan, R.: Un cas de paralysie de fonctions d'élévation, d'abaissement et de convergence des globes oculaires, Bull. et mém. Soc. méd. d. hôp. de Paris **37**:1172-1177, 1913.

15. Pasetti, G.: Della paralisi essenziale della convergenza, Ann. di ottal. **42**:912-926, 1913.

16. Farnarier, F.: Deux cas anormaux de paralysie de l'accomodation; l'un avec mydriase paralytique, l'autre avec paralysie de la convergence à la suite de diphtéries latentes, Marseille-méd. **50**:363-365, 1913.

17. Bollack, J.: Quelques particularités des manifestations oculaires de l'encéphalite léthargique, Ann. d'ocul. **157**:352-364, 1920.

18. Morax, V., and Bollack, J.: Les troubles oculaires de l'encéphalite léthargique, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:199-207, 1920.

19. Zentmayer, W., in discussion on Reese.[51]

Israel,[20] in 1921, reported 3 cases of convergence paralysis and pointed to the existing confusion concerning a center for convergence for which there was no proof, anatomically or pathologically. In 2 of his cases there were positive Wassermann reactions, and his concern was whether or not the condition was a lesion of syphilis and, if so, whether it was an early or a late manifestation.

Vandegraft and Losey,[21] in 1922, reported an interesting case in which paralysis of convergence and paresis of accommodation followed a severe roentgen ray burn of the occiput. Diplopia was present for both far and near vision, and the patient was made comfortable with a 2 degree prism, base in, before each eye for distance and a 7 degree prism, base in, before each eye for near vision. The patient was given two pairs of glasses, one with + 1.00 spheres for distance and the other with + 3.50 spheres for near vision.

Zentmayer [19] stated that convergence paralysis is a rare condition and that the case was the only one he had encountered. In the opinion of both Reese and Zentmayer the condition resulted from a small central hemorrhage, probably in the region of the quadrigeminal bodies and the cerebellum. An interesting fact was that recovery began coincidentally with the use of homatropine for refraction.

Hay,[22] in 1924, reported a case of convergence paralysis with preservation of accommodation following an attack of influenza. After several months some of the convergence returned.

Barré and Metzger,[23] in 1924, reported a case of paralysis of convergence associated with paralysis of movements of verticality in which a tumor was found in the region of the corpora quadrigemina.

In De River's [24] case the condition was associated with bilateral paralysis of the abducens nerve. The reaction to a Wassermann test of the spinal fluid was positive, and he considered the site of the lesion as nuclear.

It is interesting to note that prior to the World War the etiologic factors suggested did not include much more than vascular lesions leading to complex paralyses, cerebral tumors, especially in the region

20. Israel, J. P.: Paralysis of Convergence: Report of Cases, Am. J. Ophth. **4**:856-857 (Nov.) 1921.

21. Vandegraft, G. W., and Losey, R. R.: Paralysis of Convergence and Paresis of Accommodation, Arch. Ophth. **51**:405-407, 1922.

22. Hay, P. J.: Case of Paralysis of Convergence with Preservation of Accommodation, Tr. Ophth. Soc. U. Kingdom **44**:408, 1924.

23. Barré, J. A., and Metzger, O.: Paralysie des movements associés de verticalité et de convergence avec areflexie pupillaire et troubles cérébelleux par tumeur de la région des tubercules quadrijumeaux, Rev. d'oto-neuro-ocul. **9**: 699 (Nov.) 1924.

24. De River, J. P.: Bilateral Abducens Paralysis Associated with Paralysis of Convergence, M. J. & Rec. **124**:553-555 (Nov. 3) 1926.

of the quadrigeminal bodies, and multiple sclerosis. With widespread epidemics of encephalitis during and following the war, the number of cases and published articles multiplied.

Netter,[25] in 1918, was one of the first to report cases of this condition associated with encephalitis lethargica. Bollack[17] and Morax and Bollack[18] reported cases in 1920; Duverger and Barré,[26] in 1921; Terrien and Veil,[27] in 1926, and Bailliart and Blum,[28] in 1927.

ETIOLOGY

At the present time, the etiology of paralysis of convergence seems to be dominated by encephalitis and postencephalitic parkinsonism.

Parsons,[29] in an analysis of 1,250 cases of epidemic encephalitis, reported in England and Wales during 1919 and 1920, found ocular disturbances in 75 per cent of the cases. Duverger and Barré[30] found motility disorders in 87 per cent of cases.

Rea[31] stated that at one time encephalitis lethargica was characterized by the motor apparatus of the eye being affected. He called attention to a statement of McGowan and Cook: parkinsonism plus ocular symptoms means chronic lethargic encephalitis, whereas parkinsonism without ocular symptoms points to arteriosclerosis or one of the less usual causes of parkinsonism.

Bielschowsky[32] stated that epidemic encephalitis is responsible for 14 per cent of all ocular paralyses.

What, then, is the incidence of convergence paralysis in encephalitis lethargica, and at what stage of the disease does it develop?

---

25. Netter, A.: L'encéphalite léthargique épidémique, Paris méd. **2**:81-86 (Aug. 3) 1918.

26. Duverger, C., and Barré, A.: Troubles de l'appareil oculaire chez les Parkinsoniens, Arch. d'opht. **39**:577-578 (Oct.) 1921.

27. Terrien, F., and Veil, P.: Troubles de la convergence et de la motilité pupillaire, séquelles d'encéphalite épidémique (observation no. 1), Arch. d'opht. **43**:709-713 (Dec.) 1926.

28. Bailliart, P., and Blum, J.: Crises oculaires toniques latérales et paralysie de la convergence d'origine encéphalitique, Bull. Soc. d'opht. de Paris, February 1927, pp. 66-70.

29. Parsons, A. C.: Report on Encephalitis Lethargica, Ministry of Health, Reports on Public Health and Medical Subjects, no. 11, London, His Majesty's Stationery Office, 1922.

30. Duverger, C., and Barré, J. A.: Troubles des movements associés des yeux chez les tabétiques, les Parkinsoniens, dans l'encéphalite épidémique et chez les labyrinthiques—essai pathogénique, Rev. neurol. **5**:439-454 (May) 1921.

31. Rea, R. L.: Neuro-Ophthalmology, St. Louis, C. V. Mosby Company, 1938, p. 175.

32. Bielschowsky, A.: Lectures on Motor Anomalies: XI. Etiology, Prognosis and Treatment of Ocular Paralyses, Am. J. Ophth. **22**:723-725 (July) 1939.

As regards the incidence of convergence paralysis in cases of encephalitis, Blum [33] recorded some interesting statistics in his thesis, as follows:

Of 63 cases of lethargic encephalitis, Reys showed that in 36 per cent pure convergence paralysis was present and in 55 per cent other paralyses were associated. Cords-Blanke found convergence paralysis associated with some other paralysis in 75 per cent of 44 cases. In Kholina's series of 25 cases convergence in association with other paralyses was lacking in 96 per cent. Warchawsky observed pure convergence paralysis in 34 per cent of his series of 29 cases.

Encephalitis lethargica is usually accompanied by mild headache, and, as Rea [34] pointed out, the picture is unmistakable when there is a sudden visual disturbance, such as diplopia, with slight fever and gradually increasing lethargy. In the acute stage of the disease the individual ocular muscles are more prone to be affected. Rea [35] asserted that he had seen several patients showing, as a sequel to the disease, a deficient power of convergence, with retention of conjugate movements to the right and left.

Bussy [36] also pointed out that paralysis of convergence is less frequent at the onset and during the height of encephalitis lethargica and that the disorders of convergence increase at the time the parkinsonian symptoms develop.

According to Bielschowsky,[32] about 55 per cent of all ocular paralyses prior to 1923 were due to syphilis and metasyphilis; less than 30 per cent are now attributed to this cause, as a result of the modern therapy of syphilis, and pure convergence paralysis has seldom been ascribed to syphilis. In 30 cases of tabes Spiller and Posey [37] reported the convergence reaction absent but once and impaired twice. They mentioned a series of 77 cases reported by Rochon, Duvigneaud and Heitz in which there was loss of convergence in only 3.

Bielschowsky [38] called attention to the fact that convergence paralysis of organic origin is rare. Many reported cases, he stated, are instances of functional disturbances. The great difficulty in distinguishing them, he declared, is due to the fact that convergence is one of the fusion movements and the only one that can be performed voluntarily. The fusion tendency, together with the ability to converge, is more or less

33. Blum, J.: Contribution à l'étude du syndrome oculo-moteur tardif de l'encéphalite épidémique, Thesis, Paris, no. 46, 1928, p. 20.

34. Rea,[31] p. 500.

35. Rea,[31] p. 176.

36. Bussy, J.: Les paralysies de la convergence, J. de méd. de Lyon **16**:207-213 (March 20) 1935.

37. Spiller, W. G., and Posey, W. C.: The Eye and Nervous System, Philadelphia, J. B. Lippincott Company, 1906, pp. 504-505.

38. Bielschowsky, A.: Lectures on Motor Anomalies: X. Supranuclear Paralyses, Am. J. Ophth. **22**:603-613 (June) 1939.

diminished or absent in cases of strabismus acquired in early childhood. In myopic persons who do close work without glasses convergence is frequently defective or absent in spite of good vision in both eyes.

Bielschowsky [38] also pointed to cases reported as instances of true convergence paralysis in which the condition was nothing more than functional neurosis, encountered frequently in anemic and delicate persons or in patients convalescing from exhaustive illnesses, or a symptom of general neurasthenia or hysteria. These cases are classified wrongly, he maintained, because no effort was made to produce convergence beyond the usual methods, which frequently do not supply the required impulse to look at the near object. This can be determined further, he asserted, by watching the accommodation and the pupils during the tests. If the pupils contract and the refraction increases according to the distance of the near object, one can be certain that the deficiency of convergence is due to an organic lesion.

Zentmayer [19] and Bielschowsky [38] both described a simple method whereby functional convergence paralysis can be differentiated from the organic type by the presence of a considerable, if not entirely normal, convergence power. The subject's adduction power with prisms is examined, and in the case of convergence paralysis of organic origin crossed diplopia will arise as soon as a prism, base out, is held before one eye. In the case of functional deficiency of convergence binocular single vision will remain, and the eye behind the rotary prism will move in accordance with the increasing strength of the prism until the limit of the adduction range is passed.

ANATOMY AND PHYSIOLOGY

A study of convergence paralysis requires a review of the anatomy and physiology involved.

Distant objects are viewed binocularly by parallel and equal movements of the eyes. In near vision, opposite or nonparallel movements are necessary to obtain corresponding images on both maculas. The eyes are thus made to converge. The movements in the first instance are said to be conjugate, while those of convergence are disjunctive.

Clinically, the internal rectus muscles can cease to function in conjugate lateral movements but at the same time respond in convergence. Not only is it reasonable to assume that this ability to converge can be lost with a retention of all conjugate lateral movements, but this is an actual fact. The existence of a center for convergence is a logical assumption. It is not positively known where this convergence center is located.

Convergence is not a simple movement to be explained by a center acting on two internal recti. One must associate the question of tonus with the question of motility. This is particularly important to an understanding of the occurrence of postencephalitic parkinsonism. Stimu-

lation of any voluntary muscle also produces inhibition of tonus of the antagonist, and inhibition of the tonus of a voluntary muscle produces hypertonus of the antagonist. Thus, in convergence, there is not only simultaneous contraction of the two internal recti but also inhibition or modification of the tonus of the external recti, without influence on the action of the other muscles of the eye, as well as accommodation and a pupillary reflex.

An interesting factor, which emphasizes the intimacy which exists between the pupillary reflex in convergence and accommodation and the pupillary reflex to light, is the paths of these reflex arcs. This complexity, already considerable, is further increased by the fact that the associated movements may be not only of voluntary but also of automatic-reflex nature. From this one can easily see the necessity of some understanding of the motor paths, and in particular the paths or centers of association.

Duke-Elder,[39] in assuming the existence of a center subserving convergence, referred to a report of Wilbrand and Saenger (1921) that a nucleus with this function was located in the central gray matter near the superior colliculus. He was also in accord with the assumption of Brouwer (1918) that Perlia's nucleus is concerned.

Brouwer's [40] patient showed during life paresis of the internal recti and after death a distinct loss of cells in the nucleus of Perlia. This, he thought, favored Knies' theory that the convergence center is situated in this nucleus.

Bing's [41] scheme for the oculomotor nerve shows how the separate muscles supplied by the nerve are represented by separate nuclear groups in the area of origin. As seen in figure 1, the larger-celled, lateral portion contains the centers that supply the extrinsic muscles of the globe. On studying the diagram, one will note that the fibers supplying the levator and the superior rectus muscle arise from the nucleus of the same side; those supplying the inferior rectus arise from that of the opposite side, while those supplying the internal rectus and the inferior oblique muscle originate in the nuclei of both sides.

Lying medial to the outer portions of each nucleus is a small-celled nucleus, the nucleus of Perlia. Whitnall [42] stated the belief that fused

39. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1936, vol. 1, p. 288.

40. Brouwer, B.: Klinisch-anatomische Untersuchung über den Oculomotoriuskern, Ztschr. f. d. ges. Neurol. u. Psychiat. **40**:152-189, 1918; abstracted, Am. J. Ophth. **4**:475-476 (June) 1921.

41. Bing, R.: Compendium of Regional Diagnosis in Affections of the Brain and Spinal Cord, ed. 6, translated from the German by F. S. Arnold, St. Louis, C. V. Mosby Company, 1927, pp. 127-128.

42. Whitnall, S. E.: The Anatomy of the Human Orbit and Accessory Organs of Vision, ed. 2, London, Oxford University Press, 1932, p. 407.

into the central nucleus of Perlia is that part of the lateral portion of each nucleus which is associated with the medial rectus in subserving its function of convergence in near vision. To substantiate such a claim, he explanied that this part is the last portion of the oculomotor nucleus to be differentiated and marks the appearance in the primate series of the function of convergence. Bing [43] stated that Perlia's nucleus innervates both internal recti and controls convergence.

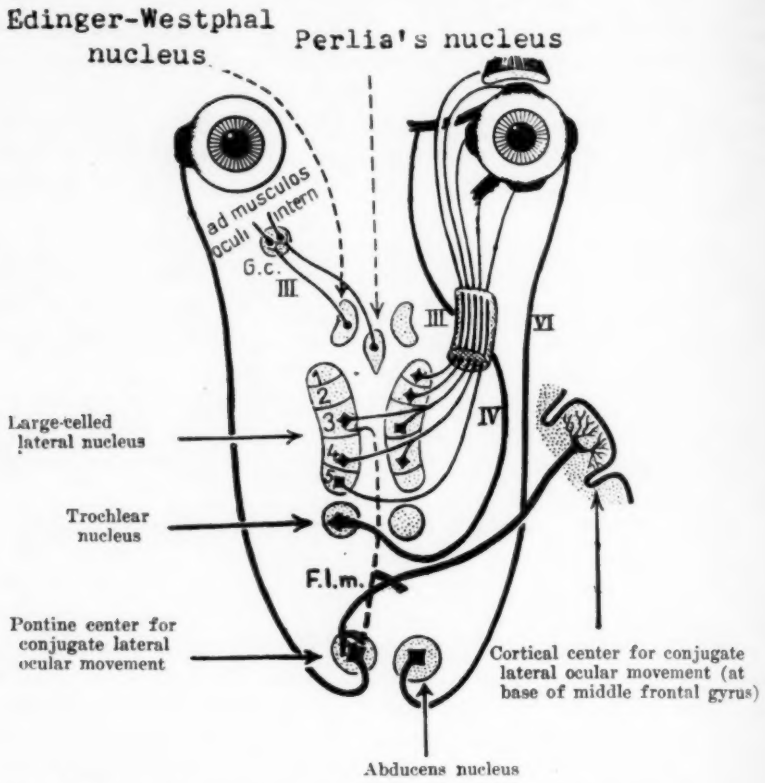


Fig. 1.—Innervation of the ocular muscles (Bing [41]). III, oculomotor nerve; IV, trochlear nerve; VI, abducens nerve; G.c., ciliary ganglion; F.l.m., fasciculus longitudinalis medialis; 1, nucleus of levator palpebrae superioris; 2, nucleus of rectus superior; 3, nucleus of rectus medialis; 4, nucleus of obliquus inferior; 5, nucleus of rectus inferior.

The small-celled lateral nucleus lies forward and on each side. It is known as the Edinger-Westphal nucleus. Tilney and Riley [44] stated that

43. Bing, R.: Text-Book of Nervous Diseases, ed. 5, translated from the German by W. Haymaker, St. Louis, C. V. Mosby Company, 1939, p. 65.

44. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 3, New York, Paul B. Hoeber, Inc., 1938, p. 427.

it supplies fibers to the ciliary muscle and the muscle of the sphincter iridis, that it is connected directly with the superior colliculus, thus mediating both the direct and the consensual light reflexes, and that it is essential to the reflexes of accommodation and convergence.

The existence of a supranuclear apparatus has universal acceptance. In fact, as Berens [45] pointed out, the diagnosis of a supranuclear lesion is based chiefly on bilateral and equal paralysis of associated groups of muscles. Coutelas,[46] in his thesis, placed the coordinating center of convergence in the so-called supranuclear center. Alajouanine and Thurel [47] also stressed the existence of a supranuclear center for the different voluntary and reflex activities of the eye and pointed out that even if there are centers of association above the nuclei of the base, the paths of internuclear association, represented chiefly by the posterior longitudinal bundle, are not well known.

Bielschowsky [38] pointed to the fact that convergence paralysis is frequently caused by lesions within the region of the corpora quadrigemina and assumed that some subcortical convergence center is located in that region. An isolated lesion, he stated, of this center or of the pathway descending to the nuclei of both internal recti must produce the symptoms of pure convergence paralysis. Duane, Lutz, Spiller and others are not in agreement with the necessity of a subcortical association center.[48] According to Duane,[48] Lutz's theory is that the descending paths from this supranuclear apparatus in the cortex pass directly to the nuclei themselves, while in the opinion of Wilbrand and Saenger they enter a lower association center.

Duane [48] divided the cerebral association centers into a frontal, an occipital and a temporoparietal center. The frontal lobe contains, in his opinion, the chief center for conjugate and the other associated movements. The frontal center is situated at the base of the second frontal gyrus, from where its efferent paths descend through the internal capsule, decussate in the brain stem and, in great part at least, enter the posterior longitudinal bundle. Ascending and descending here, they reach the third, sixth and probably the fourth nerve nuclei. It is only on bilateral stimulation of this zone that a purely vertical movement or one of convergence can be secured. Unilateral stimulation results in lateral movements only.

---

45. Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 957.

46. Coutelas, C.: Essai sur la coordination des mouvements des yeux à l'état, normal et à l'état pathologique, Thesis, Paris, no. 207, 1908.

47. Alajouanine, T., and Thurel, R.: Révision des paralysies des mouvements associés des globes oculaires, Rev. neurol. **1**:125-169 (Feb.) 1931.

48. Duane, A.: The Associated Movements of the Eyes: Their Nerve Centers, Conducting Paths, Production, Varieties, and Derangements, Am. J. Ophth. **7**:16-26 (Jan.) 1924.

The occipital center lies close to the visual centers on the median, lateral and tentorial surfaces of the occipital lobe. The visual fibers, ascending through the optic radiation to the primary visual centers, form the afferent paths for this center. The efferent paths descend through the optic radiation and join the descending paths from the frontal centers.

The temporoparietal centers have been located in the supramarginal, the superior temporal and the angular gyri. They seem to serve on the afferent sensory paths crossing from the labyrinth, the cerebellum and the region supplied by the trigeminal nerve, transmitting their impulses to the frontal especially and probably in part also to the occipital centers.

The frontal lobes are the accepted centers for willed movements. The internal recti are the only ocular muscles possessing two functions at the command of the will: the one in lateral movements of the eye and the other in convergence. The response of this center to auditory and sensory impulses from the temporoparietal region can hardly be disputed.

The occipital centers respond to the visual stimuli transmitted through the optic radiation. In fact, binocular vision depends on this intimate association between the sensorial and the motor apparatus of the eyes. When a close object is looked at, an excitation is set up on the temporal side of each retina and the stimulus results in convergence of the eyes. By their resultant movements, peripheral retinal images are transferred to the maculas, where they can be clearly seen. The fact that convergence is not voluntarily present in the blind seems to suggest the fact, according to Tilney and Riley,[44] that an important suprasegmental connection is concerned. The phenomenon certainly suggests, in their opinion, that visual attention is essential to the production of this movement and that the act of convergence necessary to near vision is in large part accomplished through a connection of the visual cortex with the superior colliculus.

Duane [48] pointed out how Wilbrand and Saenger in their late experiments came to the conclusion that fusion and attraction movements result from such stimuli. Indeed, convergence can well be called one of the fusion movements. The various fusion movements contribute much to the perfection of binocular vision. Strabismus can hardly occur when there is a good fusion mechanism.

The experiments of Sherrington, as Duane [48] pointed out, prove conclusively that the supranuclear centers discharge not only impulses of excitation but also of inhibition. Sherrington tenotomized all the muscles except the external recti and then with bifrontal cortical stimulation produced a movement of convergence which could be due only to a relaxation impulse transmitted to the external recti.

Granting the general acceptance of the supranuclear centers of association, the paths of internuclear association, represented chiefly

by the posterior longitudinal bundle, are not well known. There are other points of entry to the nuclei besides the posterior longitudinal bundle, for lesions of it affect lateral movements only—not movements of verticality, convergence or divergence. The paths for these actions are unknown, but there are sufficient physiologic and clinical data to justify the claim that the cerebral centers for them, and the descending paths as well, must be bilateral. Certain crossed anastomoses between the two posterior longitudinal bundles must insure muscular synergy.

Experimentally, the necessity for bilateral, or bicerebral, stimulation to produce these functions has been pointed out. Clinically, it is well known that unilateral cortical and subcortical lesions do not cause their abolition.

Bielschowsky [49] reported a case in which adduction was absent only in conjugate parallel movements and was unimpaired in convergence. The lesion was thought to be due to a hemorrhage in the posterior longitudinal bundle between the sixth and the third nerves, and he assumed it was when the function of the internal recti was fully restored in five weeks after absorption of the hemorrhage.

At will the internal recti can respond in parallel lateral movements of the eyes and in convergence. Both these functions, as well as only one, can be destroyed, according to the location of the lesion. The loss of both functions without involvement of other muscles supplied by the third nerve is rare. The loss of adduction only in conjugate parallel movements is rare, whereas the loss of the convergence function alone is more frequent.

PATHOLOGIC ANATOMY AND PATHOGENESIS

The complex nature of the physiology and anatomy of the movements of convergence renders a study of its pathogenesis most difficult. Autopsy has never revealed a precise anatomic lesion. In cases of neoplasm involvement is always seen in the region of the quadrigeminal bodies; but the localization is indefinite, and the paralysis of convergence is associated sooner or later with other paralyses. In encephalitis, in which the lesions are more delicate, one might expect to find better localized lesions, but this does not appear to be the case. All investigators have recognized this inability to fix an encephalitic localization. Bielschowsky [32] stated that it is easy to conceive how intracranial disease, anomalies of blood vessels and acute infectious diseases can produce convergence paralysis. He added, however, that the literature reveals nothing to substantiate it.

49. Bielschowsky, A.: Lectures on Motor Anomalies: IX. Oculo-Motor Nerve Paralysis and Ophthalmoplegias, Am. J. Ophth. **22**:496 (May) 1939.

SYMPTOMS

The symptoms of convergence paralysis are manifested by the study of ocular motility and in particular by examination for diplopia with a red glass before one eye.

The patient with convergence paralysis is unable to converge, whereas the internal recti function normally in movements to the right and to the left. Care should be taken in giving the patient the required impulse to look at the near object. The examination should be made in all directions, not only in the horizontal axis but also upward, downward and laterally. The patient's head should be kept immobile, and he should follow with both eyes open the object which is progressively approximated to his face.

There is crossed diplopia of near objects, whereas objects at a distance of more than a meter or so are seen singly, provided the convergence paralysis is not complicated by exophoria. Bielschowsky [38] pointed out that even a slight degree of exophoria will cause insuperable crossed diplopia even of distant objects in the absence of convergence. The space between the images is relatively small and varies little, if any, in lateral movements. It may increase when vision is directed upward and decrease slightly when vision is directed downward.

Opinion varies as to what pupillary signs may or may not be present. Parinaud [8] stated the belief that the following three main symptoms are necessary requisites to convergence paralysis: (1) abolition of convergence and appearance of diplopia; (2) paresis of accommodation (it is the exception for the accommodation to remain unaffected) and (3) abolition of the pupillary reaction of convergence, the reaction to light remaining. He distinguished between two forms,[8] an essential and a combined. In regard to the essential form he pointed out the fact that the pupillary reflexes are modified, and in a characteristic manner. The reflex is abolished for convergence and retained for light, an exact inverse to the Argyll Robertson pupil as occurring in tabes.

Fuchs [50] in describing convergence paralysis stated that the convergence reaction of the pupil is absent. In Reese's [51] case the pupils were unequal and active to light but did not react in accommodation or in attempted convergence, and there was no paralysis of accommodation.

Bielschowsky,[38] on the other hand, related that the convergence reaction of the pupils must be producible without the corresponding convergence. This opinion seems rigid and is not supported by all writers and observers. In reviewing reported cases, one finds variations from integrity of the pupillary reflex to diminution or absence of contractions.

---

50. Fuchs, E.: Text-Book of Ophthalmology, translated by A Duane, ed. 6, Philadelphia, J. B. Lippincott Company, 1919, p. 784.

51. Reese, W. S.: Paralysis of Convergence, Tr. Am. Acad. Ophth. **28**:262-266, 1923.

Bielschowsky [38] stated that in every case of true organic convergence paralysis these four requisites must be met:

1. There must be definite symptoms of an organic intracranial disease. 2. The convergence paralysis must have occurred rather suddenly. 3. The symptoms and signs tested at various times and by various methods must, in a certain measure, be constant. 4. The accommodation and the convergence reaction of the pupils must be producible without the corresponding convergence.

PROGNOSIS

In the majority of cases, convergence paralysis remains fixed and frequently develops in the direction of divergent strabismus. Rea [31] stated that the defect of convergence seen in connection with lethargic encephalitis remains permanently.

TREATMENT

Medically, the only treatment for convergence paralysis would be the treatment of its cause, whether tumor or infection. One surely is never criticized, however, when one treats indicated causes in any case. Surprising results may be seen with antisyphilitic therapy in a case in which positive reactions to Wassermann and Meinicke tests have been obtained. Again, in a case of convergence paralysis in which the cause is obscure one may secure surprising results with the use of diaphoretics, mercury, iodine or other medicaments.

As regards ocular treatment, if the diplopia is very disturbing, an opaque glass can be worn, and later, when the paralysis has become stationary, reeducation of the binocular vision can be tried.

Surgical intervention is rarely indicated, chiefly perhaps because it is rarely successful. Rea [31] stated that if a divergment strabismus arises as a consequence of the convergence paralysis, one should not hesitate to correct it by means of any of the orthodox operations for squint. Bielschowsky [32] pointed out, however, that in patients with paralytic conditions surgical intervention should never be attempted before six months. There are too many instances, he maintained, in which patients begin to show improvement after six months.

Thus the ophthalmologist remains relatively helpless when confronted with a case of convergence paralysis. True, declared Spaeth,[2] there are two means of alleviating the diplopia: first, the patient's spontaneous suppression in one eye; second, and especially for an older patient, the correction of the diplopia for near vision with prisms. Unfortunately, this, as well as the practice of wearing an opaque glass, is not always a successful procedure. Further knowledge of the etiology and pathogenesis of the condition should lead to more efficient treatment.

REPORT OF A CASE

B. K., a white boy aged 13, was first seen in the outpatient clinic at the Wills Hospital on March 20, 1940. His only complaint was diplopia of near objects, of two months' duration.

His tonsils were removed when he was young. Two years previously he had had rheumatic fever and had been confined to his home and to the Children's Heart Hospital of Philadelphia for six months. During this period his appendix was removed. Two months before he came to the clinic—the duration of his complaint of double vision—the mother stated that the boy had been ill with the "grip" and had been confined to bed for two weeks, during which time he had a temperature of about 101 F.

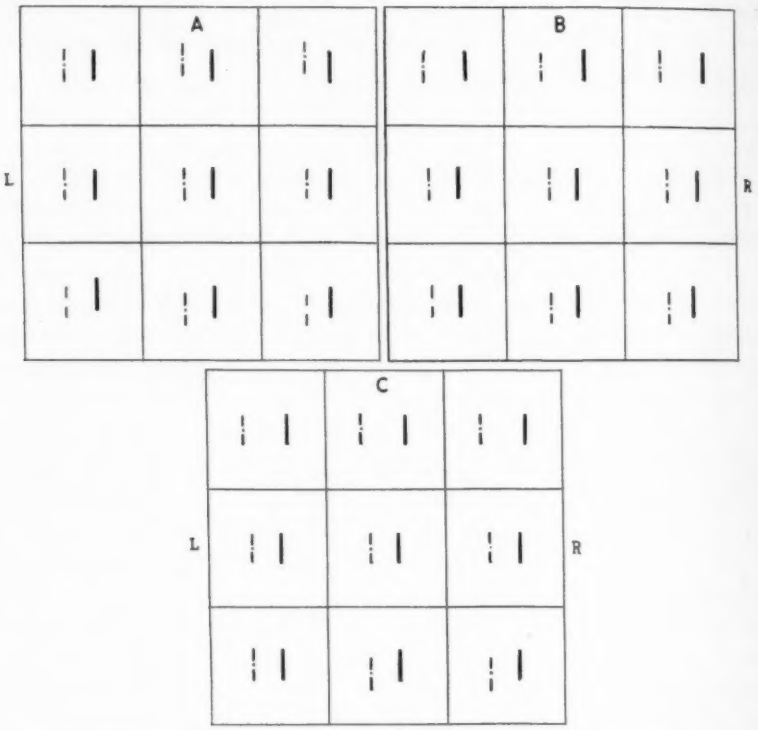


Fig. 2.—Diplopia field studies. A red glass was before the right eye. The broken line identifies the red image. "L" and "R" refer to the direction of the patient's projection. Scale: squares 6 by 6 inches (15 by 15 cm.). Crossed diplopia occurred. The separation between the images was small and varied little in lateral movements. *A*, March 27, 1940: Vision in the right eye was 6/5 and in the left eye 6/5 — 5. Distance to the screen, 1 meter. A slight difference in the level of the images was noted when vision was directed upward and downward. *B*, April 27, 1940: Vision in the right eye was 6/6 — 4 and in the left eye 6/5 — 5. Distance to the screen, 1 meter. The separation of the images was increased slightly when the patient was looking upward. *C*, April 27, 1940: Vision in the right eye was 6/6 — 4 and in the left eye 6/5 — 5. Distance to the screen, 33 cm. The separation of the images increased slightly when the vision was directed upward.

His vision was 6/6 in each eye without correction. Monocular movements were normal, as were the binocular movements, with the exception of convergence, which was entirely absent. The near point of convergence was approximately 7 feet (215 cm.), and objects within that distance appeared double. The patient was subjected to more than the usual impulse to converge, but to no avail.

The borders of the lids were slightly red and were covered with a few scattered, dry scales, giving the picture of mild blepharitis squamosa.

The pupils were round and regular in outline and of equal size. They reacted separately and consensually to light, and unless it was watched for carefully no reaction to the accommodation impulse could be detected. When the pupils were examined in good light, while the near point of accommodation for each eye was being measured, a perceptible contraction during the accommodative effort could be detected.

The results of ophthalmoscopic examination were negative; the media were clear and the fundi normal.

Detailed laboratory studies were made. Wassermann and Meinicke tests of the blood gave negative results. The concentration of sugar in the blood was

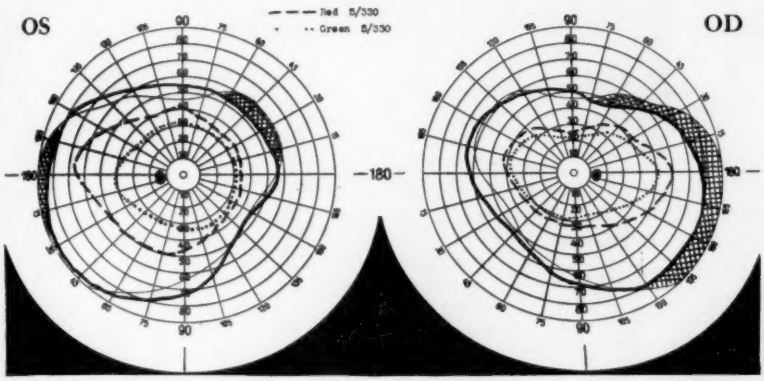


Fig. 3.—Visual fields for form and color, showing no defects. March 27, 1940: Vision in the right eye was 6/5 — 5 and in the left eye 6/5 — 5. The stimuli used were a 1 mm. white test object at a distance of 330 mm., 1, 2 and 10 mm. white test objects at a distance of 1 meter and 5 mm. red and green test objects at a distance of 330 mm.

78 mg. per hundred cubic centimeters. The urine was normal. The results of complete studies on the spinal fluid, including Wassermann and Meinicke tests, were normal. The pressure of the spinal fluid was 190 mm. and 260 mm. on coughing.

Diplopia field studies, at 1 meter, were taken a month apart, with the red glass before the right eye (fig. 2, *A* and *B*). Crossed diplopia occurred, and the separation of the images was relatively small and varied little in lateral movements. At the first examination a slight difference in the levels of the images was noted when vision was directed upward and downward. At the second examination, the separation of the images was increased slightly when the patient was looking upward. There was crossed diplopia at 33 cm. (fig. 2 *C*), with the separation of the images being again relatively small and varying little in lateral movements. The separation seemed to increase slightly when vision was directed upward. Visual fields for both form and color showed no defects (fig. 3).

Stereoscopic views of the skull showed bones of average density, with normal blood vessel markings. There was no evidence of increased intracranial pressure or of a tumor outline. Interesting, however, were the suture markings in the skull, which were certainly more prominent than usual, especially in the frontal region, just about at the point of separation. The pineal body seemed calcified

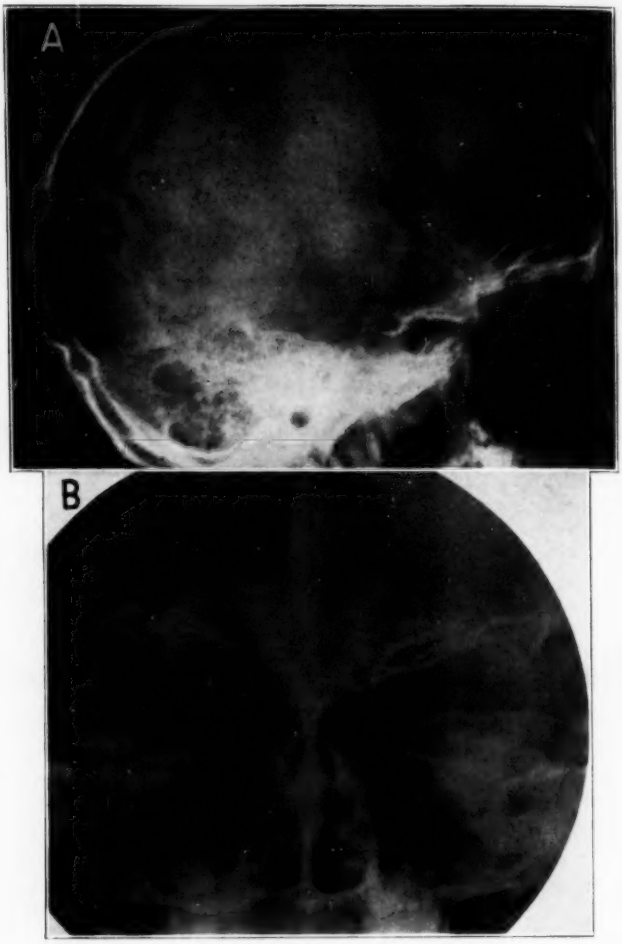


Fig. 4.—Roentgenograms of the skull. *A*, right lateral stereoscopic view. *B*, posteroanterior view of the frontal region.

but not displaced. The sella turcica was normal in all respects. The nasal accessory sinuses were essentially normal (fig. 4).

The patient was given a thorough examination in the orthoptic department. With the Maddox rod he showed 1 D. of left hyperphoria and 2 D. of exophoria at 6 meters and 20 D. of exophoria at 25 cm. With the orthoptoscope there was 2 D. of exophoria at distance and 20 D. of exophoria for near vision. With the screen and parallax test, he had 1 D. of exophoria at distance and 30 D. of exophoria for the near vision. The near point of accommodation was taken for

each eye. It measured 9 cm. (11 D.) for the right eye and 10 cm. (10 D.) for the left eye. His near point of convergence was approximately 7 feet (215 cm.). Objects within this distance appeared double.

The method described by Zentmayer[19] and Bielschowsky[38] was utilized in determining whether the convergence paralysis was functional or organic. Prisms, base out, were held before one eye. Crossed diplopia immediately occurred at 6 meters. No convergence, or adduction power, could be detected when prisms of increasing strength were placed before the eye. The eye behind the prisms remained fixed and did not move.

At the synoptophore crossed diplopia occurred and no convergence could be elicited. It was evident that the patient suppressed and did so very rapidly and without knowledge of doing so. The patient was exceptionally alert and of good intelligence and was having no trouble with his school work. He was able to read comfortably and did so through his ability to suppress, although when questioned he said he believed he was reading with both eyes at all times.

Refraction was made according to a procedure outlined by Tassman.[52] One drop of a 1 per cent solution of atropine sulfate was instilled in each eye, and, after a three minute interval, a drop of a 1 per cent aqueous solution of paredrine hydrobromide was instilled. Second drops of each of these solutions were instilled after another three minute interval. After fifty minutes, retinoscopic examination was made, and a subjective test at the trial case was done. The refractive error was found to be slight: right eye, —0.25 D. sph. —0.25 D. cyl., ax. 10 (resulting vision 6/6 + 4); left eye, 0.25 D. sph. (resulting vision, 6/6 —5).

The patient was referred to the department of internal medicine, where he was examined by Dr. Harry B. Fuller. Dr. Fuller reported that the patient's heart sounds were normal and that there was no increase in the size of the heart. He found nothing to indicate the origin of an embolus and stated the belief that the attack of "grip" that had preceded the onset of the diplopia may have been a mild form of encephalitis.

Dr. Nathan S. Schlezinger, of the department of neurology, reported that the only significant neurologic finding in the case was the paralysis of convergence. He reported, "Such findings not infrequently are sequels to encephalitis, and such a diagnosis must be seriously considered in this case."

SUMMARY AND CONCLUSIONS

A case of convergence paralysis is presented. Diplopia for near vision and the inability to converge have remained constant. Encephalitis was likely the causative factor, in view of the history of an acute illness of two weeks' duration preceding the onset of diplopia. The internist and the neurologist concurred in this opinion.

As an introduction to the presentation of this case, a brief historical survey has been given to illustrate the differences of opinion which have existed concerning convergence paralysis, together with a review of its anatomy, physiology and pathogenesis.

Convergence paralysis is a rare condition in which the paralysis remains permanently. The variety of theories and opinions concerning this anomaly clearly indicate the need of a better understanding of the anatomy and pathogenesis involved.

52. Tassman, I. S.: The Use of Paredrine in Cycloplegia, Am. J. Ophth. **21**: 1020-1021 (Sept.) 1938.

News and Notes

EDITED BY W. L. BENEDICT

GENERAL NEWS

Ophthalmologist Leaves Funds for Research.—The residuary estate of the late Dr. Walter H. Snyder, an ophthalmologist of Toledo, Ohio, which is valued at $350,000, has been released by court action for the establishment of the Snyder Ophthalmic Foundation to provide funds for research in diseases of the eye. By trust agreements made several years ago, Dr. Snyder and his wife, who died in 1937, placed the bulk of their property in trust and directed that on their deaths the funds should be used for research in ophthalmology and other charitable purposes. After Dr. Snyder's death in 1938 the will was contested by relatives. The research funds are to be administered by five directors, including Drs. Conrad Berens and John H. Dunnington, of New York, two Toledo bankers and an attorney.

Bequests of Dr. Emory Hill.—Dr. Emory Hill, emeritus professor of ophthalmology, Medical College of Virginia, who died Dec. 4, 1940, bequeathed his medical library to the department of ophthalmology at the college. Dr. Hill also left a bequest of $500 to the American Ophthalmological Society.

UNIVERSITY NEWS

Graduate Course at the New York Eye and Ear Infirmary.—The New York Eye and Ear Infirmary will hold its fifth annual postgraduate course from March 24 to 29, 1941. Lectures and demonstrations will be given daily by members of the staff of the infirmary and by guest speakers. There will be courses in ophthalmology, otology, laryngology, rhinology, bronchoscopy and esophagoscopy. The fee for the entire course is $50. The prospective registrants should address the School of Ophthalmology and Otolaryngology, New York Eye and Ear Infirmary, Thirteenth Street and Second Avenue, New York.

SOCIETY NEWS

Dallas Southern Clinical Society.—An announcement has been made regarding the thirteenth annual spring clinical conference of the Dallas Southern Clinical Society to be held March 17 to 20, 1941 at the Hotel Adolphus, Dallas, Texas. Dr. W. D. Jones, of Dallas, will preside over the Wednesday afternoon clinic on eye, ear, nose and throat. Postgraduate lectures will be given on ophthalmology. Included in the list of honor guests is Dr. Derrick Vail, professor of ophthalmology and head of the department of ophthalmology, Cincinnati College of Medicine, Cincinnati.

Correspondence

THE JACKSON CROSSED CYLINDER

To the Editor:—In a paper on the Jackson crossed cylinder (Friedman, B.: The Jackson Crossed Cylinder, ARCH. OPHTH. **24:** 490 [Sept.] 1940) the statement is made, with reference to determining the correct axis, that the simple procedure of temporarily overcorrecting the cylinder in the trial frame by 0.50 to 1.00 D. and then rotating it a few degrees to either side of the tentative axis is far less complicated and optically accomplishes exactly what the Jackson crossed cylinder does. This statement is not quite accurate; the mode of action of the several tests is different, as the following analysis will show.

The rotating cylinder method is practiced in two or three ways. One way is to rotate the cylinder from the tentative axis to the position of greatest clearness. This method may be called the blur-to-clear rotation. The end stage is the "clear" position. The other method is to rotate the cylinder from the tentative position first toward one side and then toward the other side, stopping at each turning at the point of blur (or at the point of greater blurring than that started with). This method may be called a blur-to-blur rotation. The midpoint between the two end positions is taken as the correct axis. With both these methods the end stage, whether it is the "clear" position or the "blur" position, is arrived at by a slow and gradual process. The changes in vision, whether clearing or blurring, are gradual. With the latter there is an additional difficulty, as the patient has to note, remember and compare the degree of blurring at each end of rotation.

The cross cylinder technic for the correct axis depends on a reaction to a quick and sudden change. Suppose the test cylinder is at a tentative axis of 90 degrees; then the cross cylinder moves the cylinder effect suddenly to, say, 110 degrees and by a twirl of the fingers moves it just as quickly and suddenly to 70 degrees. The patient has to compare the effect of an instantaneous change of the cylinder from 110 degrees to 70 degrees. The reaction is to a quick and sudden stimulus, and the response is generally active and easy to elicit. Suppose the test cylinder is at 90 degrees and the true axis is at 85 degrees. The cross cylinder, the effect of which is to shift the test cylinder (slightly strengthened), say, first to 110 degrees and then quickly to 70 degrees, presents two visual impressions that can be quickly compared. In these cases, vision with the cylinder axis at 70 degrees, 15 degrees off true axis, must be appreciably better than vision with the cylinder axis at 110 degrees, 25 degrees off true axis. It will be noted also that the cross cylinder doubles the error and therefore intensifies the effect; that is, when the test cylinder is only 5 degrees off true axis the effect of the cross cylinder is to compare vision with the cylinder positions differing by 10 degrees.

A third method of cylinder rotation sometimes used is to make a quick single shift from one axis position to another, say, from 90 to 95 degrees, and compare vision at the two positions. This is probably the

best of the cylinder rotation tests for suddenness of change and quick contrast. But even this is a poor substitute for the quickness and suddenness accomplished with the cross cylinder.

There is no one test either for astigmatism, axis or amount, or for any other refractive error, which works equally well in all cases. In some cases the rotating cylinder methods, blur-to-clear, blur-to-blur or single shift, or a combination of these may work best. But the cross cylinder technic has special features, such as the effect of sudden contrasts, which differentiate its mode of action from that of the others.

JOSEPH I. PASCAL, M.D., New York.

COCAINE THE IDEAL LOCAL ANESTHETIC

To the Editor:—Advertisements which appear in ophthalmic journals and literature regarding the newer local ophthalmic anesthetics contain statements seemingly finding fault with cocaine. Statements by manufacturers are so worded as to make it appear that cocaine has many disadvantages compared with the newer synthetic drugs.

Having used cocaine as a local anesthetic in the eye for the past twenty-five years, I wish to make a statement for the benefit of those with lesser experience: I find cocaine the ideal anesthetic in ophthalmic surgery.

In not a single instance did I ever find cocaine toxic to the patient when used as a local anesthetic in cataract operations. This experience is not only my own but that of my associates, with whom I have conferred about this matter. In a series of 200 consecutive cataract operations in which a 1 per cent solution of cocaine hydrochloride was used subconjunctivally and in the superior rectus muscle, I have not had a single case of cocaine poisoning.

Some manufacturers of new products find fault with cocaine in that it produces clouding of the cornea, dilates the pupil and reduces intraocular tension. I personally do not find fault with these reactions to cocaine. In fact, they have their advantages. Drying of the cornea is mentioned as though it were a permanent and dangerous complication. Ophthalmologists who use cocaine every day in their practice know that this drying is immediately dissipated by the momentary closure of the lids or by instilling physiologic solution of sodium chloride into the eye at the time of operation. In a determination of the intraocular tension I prefer phenacaine hydrochloride, not because it is superior to cocaine hydrochloride but because it has an advantage over the latter in that cocaine may reduce the intraocular tension and thus produce incorrect reading.

In all other instances in which effective anesthesia of the eyeball is to be obtained, it is my personal opinion that cocaine hydrochloride is the ideal anesthetic.

The speed of anesthesia has no particular advantage to the ophthalmic surgeon. It is completeness and effectiveness of the anesthesia that are desired.

My remarks of course do not pertain to the use of procaine hydrochloride when retrobulbar or subcutaneous anesthesia is desired.

I trust that this letter is of sufficient importance for publication, in view of the unfair criticism of cocaine, which is contrary to the experience of the busy ophthalmologist.

LOUIS LEHRFELD, M.D., Philadelphia.

TREATING DACRYOCYSTITIS IN THE NEWBORN

To the Editor:—In the December 1940 issue of the ARCHIVES (**24:** 1256 [Dec.] 1940) is a clinical note entitled "A Simple Method of Treating Dacryocystitis in the Newborn" by Archimede Busacca.

For many years I have probed the tear drainage apparatus in children with this condition, being certain that the probe gets into the nose and that it is not covered with mucous membrane. I have never seen this method fail, and I very rarely found more than one probing necessary. I doubt very much the advisability of injecting a fluid into the lacrimal sac with as much pressure as possible.

Several years ago this multiple flushing was described at a meeting of the Eye, Ear, Nose and Throat Section of the Illinois State Medical Society (I cannot remember by whom). I well remember that Dr. Harry Woodruff, of Joliet, Ill., and I discussed the presentation and that his experience in the treatment of dacryocystitis in infants coincided with mine.

Ordinarily the management of this condition is so simple that I dislike to see it made complicated and prolonged.

G. HENRY MUNDT, M.D., Chicago.

Questions and Answers

BUFFER FOR OPHTHALMIC SOLUTIONS

To the Editor:—What is the formula for the buffer to be added to the usual solutions prescribed for use in the eye, especially physostigmine salicylate and zinc sulfate solutions? Has the use of a buffer been proved of advantage?

A. R. C., M.D., Louisiana.

Answer.—In 1928 or before, it was recognized in Europe that the hydrogen ion concentration (p_H) of a solution has more to do with the sensations produced when the solution is dropped into the eye than has its osmotic pressure. The same is true of the untoward effects on the conjunctiva of the protracted use of drugs in solution. The importance of the subject was pointed out in the United States by S. R. Gifford and R. D. Smith (Effect of Reaction on Ophthalmic Solutions, ARCH. OPHTH. **9:** 277 [Feb.] 1933). Chemists had long known that the p_H of a solution could be controlled by suitable buffering, and the principle had long been used by some oculists empirically.

When ophthalmic solutions are buffered at a desirable p_H, they can be made less irritating and more stable and in most cases can be made to promote better absorption and utilization of the dissolved drug. By the use of properly buffered solutions, the discomfort which attends instillation and the subsequent untoward conjunctival reactions may be reduced to a minimum.

The preparation of the buffer reagents and their solutions requires a knowledge of physical chemistry and the use of special apparatus and equipment. There are few pharmacists who specialize in this work and who are capable of buffering correctly the preparations used by the ophthalmologist. Many ophthalmologists who have become interested in buffer solutions have been discouraged by the lack of results from solutions prepared by pharmacists who were not thoroughly trained in this field.

In the determination of the p_H of solutions, several methods may be utilized. The colorimetric p_H methods have played an important role under certain conditions. Their usefulness is limited. The addition of dye to an unbuffered solution is likely to change the p_H of the solution.

The best method in the hand of a skilled operator is the electrometric. High accuracy may be obtained by use of a p_H meter in conjunction with the glass electrode. The hydrogen electrode technic has been highly developed, so that an accuracy down to p_H + — 0.001 is obtainable under ideal conditions. This has been shown by such workers as Goyon, Barnes and Hind (*Indust. & Engin. Chem.* [*Analyt. Ed.*] **12:** 185 [Aug. 15] 1940).

In buffering solutions at different points on the p_H scale, several different buffer systems must be employed. The three principal buffer systems which have been particularly useful are:

	p_H
1. Sodium acetate–acetic acid buffer	3.7 to 5.6
2. Sodium acid phosphate–disodium phosphate buffer	5.9 to 8.0
3. Sodium borate–boric acid buffer	6.8 to 9.2

Each alkaloidal salt, heavy metal, acid or basic salt is a problem in itself. It is impossible to enter into the chemical aspects of buffering all ophthalmic preparations here, but some examples will serve as illustrations.

A solution of epinephrine hydrochloride should not be buffered much above a p_H of 5.0, because it is readily oxidized at high p_H levels, and the manufacturers have spent thousands of dollars to determine the optimum p_H for this substance. It, therefore, should be used as it is obtained from the pharmaceutic houses.

If an attempt is made to buffer a solution of zinc sulfate at a level above p_H 5.2 the zinc is quantitatively precipitated in the form of zinc hydroxide. In dilute solutions the precipitation is not obvious, because the zinc hydroxide is precipitated in the colloidal form and the solution is apparently clear to the eye. However, if the action of the zinc ion is desired by the ophthalmologist the p_H must be at a level below 5.2. Such a solution is certain to smart and burn.

If the p_H of a solution of physostigmine salicylate is raised above 6.8 the free alkaloidal base is liberated, which has an inherent irritating effect, is unstable and readily oxidizes. At a p_H of 6.8, physostigmine salicylate exists as a salt which is relatively nonirritating and stable. The tears, which are themselves well buffered, react slowly with the 6.8 buffer and produce a slow liberation of the free base; consequently the irritation commonly associated with the use of physostigmine salicylate drops is abolished or greatly diminished.

From these examples it will be seen that one cannot make a single buffer solution and dissolve all ophthalmic drugs in it. As the drug dissolves, it disassociates, and the p_H finally attained by the solution is a resultant of all the ionic forces present and is almost certain to be different from the original p_H of the buffer solution. Unless the buffer is properly selected, the final solution may be no more suitable than if the usual practice of dissolving the drug in distilled water had been followed. The results that can be attained by the intelligent use of the principle are worth all they cost in care, effort and time; the expense is small.

EXCRETION OF SULFANILAMIDE IN BREAST MILK

To the Editor:—I was called to treat a baby 4 days old for gonorrheal conjunctivitis. The baby's mother was taking at this time large doses of sulfanilamide. The question arose as to whether or not the sulfanilamide taken by the mother would be transmitted through the breast milk to the baby. This baby was a white first-born girl, and the mother had had a low forceps delivery. There were no injuries except for a small hematoma at the left upper parietal region of the scalp. The weight was 2,800 Gm. (6 pounds, 3 ounces). There were full use of the limbs, a lusty cry and a good appetite. There was no evidence of ill health except for swollen and inflamed eyes. I began to give the infant an initial dose of 0.32 Gm. of sulfanilamide in water per kilogram of body weight per day. The next day I increased the dose to 0.65 Gm. per kilogram per day, and after the third dose the baby's skin had a blue tinge, which lasted two hours. The next day the original dose was administered again, and the child has not shown any untoward effects since. I have used the sulfanilamide and sodium bicarbonate combination, and there has

been no rash. The inflammation and swelling of the lids nearly all disappeared by the fourth day; the secretion is still fairly free, with no traces of blood, and there is no evidence of injury to the corneas.

I have treated many small children between the ages of 1½ to 4 years with sulfanilamide for gonorrheal conjunctivitis, with the usual quick recovery of the eyes, but this is the first nursing baby that I have ever treated whose mother was taking sulfanilamide at the same time.

What quantity of sulfanilamide is carried by the mother's breast milk to the baby, and what allowance in dosage for the baby should be made?

J. J. C., M.D., Mississippi.

Answer.—Sulfanilamide is excreted in human breast milk in concentrations which vary but usually approximate 80 per cent of the concentration of the drug in the blood. With average doses of sulfanilamide which might be given to a lactating mother it would be unusual for the baby to obtain as much as 1 grain (0.06 Gm.) of the drug in twenty-four hours from the breast milk, and therefore this factor would play no appreciable role, as a rule, when nursing infants are being treated with sulfanilamide. References in this regard may be obtained in the following articles:

Foster, F. P.: Excretion of Sulfanilamide in Breast Milk: Report of Case, Proc. Staff Meet., Mayo Clin. **14:** 153-155, 1939.

Hac, L. R.; Adair, F. L., and Hesseltine, H. C.: The Excretion of Free and Acetylsulfanilamide in Human Breast Milk, Am. J. Obst. & Gynec. **38:** 57-66 (July) 1939.

Pinto, S.: Excretion of Sulfanilamide and Acetylsulfanilamide in Human Milk, J. A. M. A. **111:** 1914-1916 (Nov. 19) 1938.

Stewart, H. L., Jr., and Pratt, J. P.: Sulfanilamide Excretion in Human Breast Milk, and the Effect on Breast-Fed Babies, J. A. M. A. **111:** 1456-1458 (Oct. 15) 1938.

Adair, F. L.; Hesseltine, H. C., and Hac, L. R.: An Experimental Study of the Behavior of Sulfanilamide, J. A. M. A. **111:** 766-770 (Aug. 27) 1938.

OPHTHALMIC DEVELOPMENT IN INFANTS

To the Editor:—At what age should an infant be attracted by light and follow the light with his eyes? At what age should an infant be attracted by objects? At what age should an infant recognize objects? At what age should binocular vision develop?

S. G., M.D., Pennsylvania.

Answer.—The normal infant will usually show evidence of the light sense at birth by closing the eyes and grimacing when a flash light is turned on the eyes in a semidark room. By the end of two weeks the infant will often turn the eyes momentarily toward a bright light.

The first signs of any attention being paid to form occurs about the fifth to the eighth week after birth, when the infant may stare at a large object, such as the hand, and even follow its motions with the eyes. At this time, however, the eyes may or may not move together uniformly.

Recognition of objects is hard to determine. Some psychologists claim infants show color preference at an age as early as 3 months. Probably visual memory has been sufficiently developed by 6 months to allow recognition of objects.

Binocular vision cannot be present until the binocular reflexes are established. Although vergence seems to be established by the age of 4 months, it is often later than this before the eyes move together in a well established fashion. Some degree of binocular vision may be present at this time, but since it cannot be tested, it is impossible to say that the infant really does see with both eyes simultaneously. Between the second and the third year it is usually possible to note simultaneous macular perception with some degree of certainty, but stereopsis can be ascertained only after the age of 3 years.

During the first six or seven years of life binocular vision may become a well established reflex or it may be easily abolished or never acquired, depending on the development of motor coordination and sensory association of the eyes.

OPERATION FOR MATURE CATARACT WITH CHRONIC GLAUCOMA

To the Editor:—For a patient with a mature cataract and with chronic glaucoma under control with pilocarpine hydrochloride, is it advisable to do a preliminary trephining, or would an extraction with iridectomy be adequate?

S. G., M.D., Pennsylvania.

Answer.—For a patient with a mature cataract and with chronic glaucoma which is controlled by pilocarpine hydrochloride it is generally thought advisable to combine a tension-lowering operation with the cataract extraction. If the glaucoma is of the chronic noncongestive type, an iridectomy alone is unlikely to have any permanent effect on the tension. An iridencleisis appears to be preferable to a trephine operation, because of the fistula produced by an incarcerated piece of iris is less likely to close up during the inflammatory reaction following cataract extraction. Furthermore, the iridencleisis can safely and conveniently be performed in the same sitting as the cataract extraction, the chances of establishing a permanent fistula with the combined operation being just as good as with a two stage operation (the iridencleisis preceding the cataract extraction by two or three weeks). Intracapsular extraction of the cataract should be attempted. Total iridectomy is definitely preferable to peripheral iridectomy or to the iridotomy done ordinarily with the iridencleisis.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Conjunctiva

CYTOLOGIC EXAMINATION AND THE PATHOGENESIS OF VERNAL CATARRH. I. MARCUS, Vestnik oftal. **15:** 16, 1939.

In 16 patients suffering from vernal catarrh the conjunctiva was scraped and a large number of young eosinophils were found (with a shift to the left in the Schilling count). The cytologic triad present, eosinophils, monocytes and histiocytes, was characteristic of vernal catarrh. This reaction speaks for an allergic pathogenesis of vernal catarrh. Further study should be directed toward the endocrinologic status and dysfunction of the vegetative nervous system of these patients.

The majority of these patients were from 7 to 13 years old, and only 5 were adults. A review of the literature is given.

O. SITCHEVSKA.

Cornea and Sclera

CHRYSIASIS OF THE CORNEA AS A RESULT OF SODIUM GOLD THIOSULFATE TREATMENT. ALBERTO URRETS ZAVALIA and ROBERTO OBREGON OLIVA, Arch. de oftal. de Buenos Aires **14:** 182 (Feb.) 1939.

Having observed, by slit lamp examination, in a patient with chronic tuberculous uveitis treated successfully with sodium gold thiosulfate an infiltration of shining bright spots in the cornea and having found a similar condition in other patients submitted to a similar treatment, the authors determined to investigate this condition in a series of patients of different sexes and ages from the central antituberculosis dispensary of the Central Council of Hygiene, Córdoba, Argentina, who had pulmonary tuberculosis and were submitted for the first time to this treatment in the form of injections.

During the first weeks no abnormality is manifest, but when the total amount injected reaches 1 to 3 gm. a number of fine needle-like crystals appear in the superficial layers of the cornea, apparently under Bowman's membrane. There is some difference in the time of this appearance, the given figures being an average, the lowest amount bringing this about being 0.55 Gm. and the highest 2.3 Gm. As the treatment continues the impregnation increases, being more marked in the center of the cornea and diminishing toward the periphery. Its maximum is reached when the total amount injected reaches about 4 Gm. With the continuance of the treatment with the dose totaling 3 to 5 Gm., a deep infiltration of round yellowish red granules appears at the periphery and gradually invades the whole cornea. This impregnation produces

no irritation, excepting a slight photophobia in a few instances. When the treatment is stopped the crystals gradually disappear in a few months, but the granules persist permanently.

The authors review briefly the literature on the subject and are inclined to consider the superficial infiltration as sodium gold thiosulfate and the granules as metallic or colloidal gold or gold sulfite. They do not reach definite conclusions but consider that the cornea lends itself specially to the study of gold deposits in different parts and tissues of the body during the various forms of gold treatment.

C. E. FINLAY.

Experimental Pathology

THE INFLUENCE OF TESTICULAR EXTRACT ON THE PERMEABILITY OF THE CORNEA. EXPERIMENT WITH ASCORBIC ACID. F. SCHUPFER, Ann. di ottal. e clin. ocul. **67**: 527 (July) 1939.

Testicular extract has been shown to increase the permeability of the skin, this effect being due to an R factor (Reynals), which is present in other tissues but is especially rich in the testicles. Rossi had shown a similar effect on the permeability of the cornea to alkaloids, fluorescein and potassium thiocyanate. The author employed a dried extract of beef testicle, of which 1 Gm. was dissolved in 7.5 cc. of distilled water before it was employed. When the rabbit's cornea was bathed in this solution for fifteen minutes, followed by an isotonic solution of potassium thiocyanate (1.47 per cent) for ten minutes, the aqueous was found to contain thiocyanate, as shown by a red color with ferric chloride. In controls in which saline solution was employed instead of the extract, no thiocyanate entered the aqueous, even after forty-five minutes of instillation. The extract alone produced conjunctival chemosis and also a punctate roughening of the corneal epithelium. Since the increased permeability may have been due to injury to the epithelium, experiments with ascorbic acid were employed. It was first shown that the extract alone had no effect on the reducing power of the aqueous. Instillation of a solution of ascorbic acid alone for twenty to forty-five minutes produced only a slight increase in reducing power. When testicular extract, freshly prepared, was first instilled for fifteen to twenty minutes, followed by ascorbic acid for twenty to thirty minutes, the reducing power of the aqueous was constantly increased, the average increase being 33 per cent. Removing the corneal epithelium before the experiment greatly increased the reducing power of the aqueous, but the reducing power was still greater in eyes previously bathed in testicular extract. The epithelial lesions as observed with the slit lamp were the same when ascorbic acid was employed alone or when both ascorbic acid and the extract were employed. When the extract was passed through a dialyzing membrane, a similar effect on corneal permeability to ascorbic acid was observed, though this dialysate produced no lesions of the epithelium. An increase in permeability, although less marked, was observed when twenty-four hours was allowed to pass between instillation of the extract and that of ascorbic acid.

S. R. GIFFORD.

NERVOUS CONDUCTION OF CORNEAL STIMULI IN EXPERIMENTAL LEUKOCYTOSIS. I. BORSOTTI and L. LOCATELLI, Arch. di ottal. **45:** 55 (March-April) 1938.

Borsotti and Locatelli studied the leukocytic curve in rabbits which had had mallein injected into the parenchyma of the cornea. Within fifteen to thirty minutes the leukocyte count had doubled. This increase was not present following neurolysis by retrobulbar injection of alcohol. Removal of the superior cervical ganglion had no remarkable effect on the phenomenon.

It is the opinion of Borsotti and Locatelli that the pathway of conduction of the stimulus to the blood-regulating centers to produce such a reaction must of necessity be nervous. F. P. GUIDA.

General Diseases

INVESTIGATION OF THE CENTRAL AND PERIPHERAL LIGHT SENSE IN PATIENTS WITH HEPATIC DISEASES, WITH AND WITHOUT ICTERUS. V. NAPOLEONI, Arch. di ottal. **45:** 258 (Sept.-Oct.) 1938.

Napoleoni tested the light sense of 15 patients with hepatic diseases, utilizing the light adaptation tests of Engleking and Hartung. No change in the light sense could be detected until jaundice had set in.

In view of the relation of visual purple to light sense and since visual purple is soluble in bile salts, the results are in keeping with known facts. It is also known that bile salts interfere with the regeneration of visual purple. F. P. GUIDA.

Glaucoma

THE COLOR SENSE IN GLAUCOMA. I. BARBEL, Vestnik oftal. **15:** 10, 1939.

The color sense was tested in 66 patients, or in 102 eyes. Of these, 33 eyes were affected with simple chronic glaucoma, 22 with the chronic inflammatory type, 3 with the acute form, 16 with the juvenile condition and 14 with glaucoma in the prodromal period; 10 eyes were normal in cases of unilateral glaucoma. The Ishihara, Stillings and Rabkin's pseudoisochromatic tables were used, and also the anomaloscope. Not only was the color sense examined, but Barbel also tried to find out whether this function of the eye was stable or whether it fluctuated at a given time and also whether external factors influenced these fluctuations. The pigment tables showed only the qualitative values of the color sense, while the anomaloscope established the quantitative value by the method of "double threshold." The color adaptation and the color asthenopia were also determined. The article presents a thorough study of the subject and is illustrated by a number of graphs and tables.

Barbel arrived at the following conclusions:

1. The color sense tested with the pigment tables and the anomaloscope was found to be normal in the majority of the cases of glaucoma (in 68 of 102 eyes).

2. In 34 eyes changes in the color sense were observed.

3. No parallelism was observed in a number of cases between the color sense and other functions of the eye.

4. The methods applied so far do not allow one to draw positive conclusions that the condition of the color sense can serve as an early diagnostic sign of glaucoma.

5. The color sense can be a fair indicator of the presence of vegetative shifts in glaucomatous patients, as in a number of cases distinct fluctuations of the color sense were observed after influencing the nervous system, particularly after cervical diathermy.

6. The lability of the nervous system in glaucomatous patients explains the frequency of color asthenopia in these patients.

7. All the data of these examinations allow the general conclusion to be drawn that although the static condition of the color sense is normal in the majority of the glaucomatous patients, the dynamic process shows instability and disturbance of the color sense.

Wessely's method of examination of the color sense in glaucoma will be reported later.

O. SITCHEVSKA.

Lacrimal Apparatus

ROENTGENOTHERAPY OF EPIPHORA. G. TREISER, Vestnik oftal. **8:** 30, 1939.

During the years 1931 to 1936 inclusive, roentgenotherapy was applied to 47 patients suffering from persistent epiphora after routine measures had failed. The technic of the treatment is described. The dose was from ⅓ to ⅕ unit skin dose; from two to three irradiations were sufficient to weaken the function of the lacrimal gland.

The patients were observed from twelve to eighteen months. Twenty-two eyes were cured; in 17 eyes the epiphora was only slight in cold weather, and in the others there was a recurrence of the symptoms. The roentgen rays evidently act indirectly on the nervous apparatus of the lacrimal gland, and this would explain the early impairment of the function of the gland (before atrophic changes set in).

O. SITCHEVSKA.

Lens

A CASE OF DISLOCATION OF THE LENS INTO THE VITREOUS. F. CASINI, Arch. di ottal. **45:** 39 (Jan.-Feb.) 1938.

Casini reports the case of a 71 year old man who had been struck in the left eye by a small piece of wood. Vision was lost in a few days. Examination revealed a clear cornea, an anterior chamber of normal depth, mild mydriasis and iridodonesis. The lens was dislocated downward and was freely movable, and its upper edge was visible through the undilated pupil. Slit lamp examination showed that the vitreous had herniated through the pupil. The patient was followed regularly over a period of two years. At no time did an inflammatory reaction appear. The tension remained normal. Vision with a $+11:00$ D. correction had dropped from 0.5 to 0.4. The lens was no longer movable and could be seen only after maximum mydriasis and greatest inferior rotation of the eye.

Casini states the opinion that a weakness of the fibroelastic tissues of the body must be present to allow dislocation of the lens and herniation of the vitreous following such mild trauma. For added evidence of this fact he states that his patient had a recurrent inguinal hernia, gastroptosis and bronchial asthma. The author feels that the absence of increased intraocular tension after such a long time made the case worth reporting.

F. P. GUIDA.

Lids

A CASE OF A SINGLE ORIENTAL BUTTON OF THE LID: INOCULATION OF THE LEISHMANIASIS TISSUE INTO THE EYE OF A DOG. C. TITA, Arch. di ottal. **45:** 86 (March-April) 1938.

Tita reports a case of a single oriental button appearing on the upper lid of a 65 year old woman. Three months before examination a small red ulcer appeared on the outer third of the upper lid and was followed shortly by generalized swelling of the lid. One week before she was seen a serosanguinous exudate appeared. Hot compresses did not affect the lesion. Scraping from the base of the lesion stained with Giemsa stain showed typical Leishman-Donovan bodies. Examination of smears of the circulating blood, of blood from the skin adjacent to the lesion and of the exudate gave negative results. Attempts to reproduce the lesions by inoculating the ocular tissue of dogs were unsuccessful.

F. P. GUIDA.

Neurology

SIGNIFICANCE OF THE OCULAR FINDINGS FOR THE DIAGNOSIS OF TUMORS OF THE BRAIN. E. LOBECK, Arch. f. Ophth. **140:** 599, 1939.

Observations on cases of tumor of the brain which are reported in detail lead the author to conclude that the central scotoma which is a characteristic symptom of tumor of the frontal lobe is probably caused by direct pressure of the tumor on the crossing portion of the papillomacular bundle, which is situated in the most dorsal portion of the intracranial portion of the optic nerves. In suprasellar tumors the development of choked disks is the rule, whereas intrasellar tumors practically never lead to choking of the disks.

P. C. KRONFELD.

RECKLINGHAUSEN'S NEUROFIBROMATOSIS AND THE EYE: REPORT OF A CASE. F. W. MEYER, Klin. Monatsbl. f. Augenh. **103:** 44 (July) 1939.

A man aged 29, who gave the impression of being a dull boy of 18 years, had observed a considerable enlargement of the upper lid of his right eye for several years. He had underdeveloped testicles and presented a feminine habitus. A tumor removed from the area of the shoulder blade proved to be a neurofibroma. The elephantiasis of the lid was of the same type. Aside from these tumors only two nodules in the skin were found to establish the diagnosis of Recklinghausen's neurofibromatosis and mental and endocrine disturbances. No explana-

tion could be given for an enormous enlargement of the optic canal and for a peculiar structure of the sella turcica. Photomicrographs of the tumors are added. K. L. STOLL.

Pharmacology

HISTOCHEMICAL INVESTIGATION OF THE DIFFUSION INTO THE OCULAR BULB AND ITS ADNEXA OF GOLD SALTS INTRODUCED BY VARIOUS METHODS. G. CAVALLACCI, Arch. di ottal. **45:** 1 (Jan.-Feb.) 1938.

Using the histochemical method of Lombardo, Cavallacci found that gold salts injected intramuscularly and intravenously into the white rabbit were found distributed throughout the adnexal and bulbar tissues, being especially abundant in the cornea after it had been irritated by ethylmorphine hydrochloride. After subconjunctival injection the gold salts were found in the bulbar conjunctiva, episclera, sclera and cornea and in small amounts in the iris and ciliary body. Instillation into the conjunctival sac allowed the salts to diffuse into the bulbar conjunctiva, episclera, lids and cornea.

Examination of the tissues histologically and by intravital staining showed that, as in other organs, the salts are taken up by the reticuloendothelial cells.

Cavallacci concludes that gold therapy for ocular diseases owes its value to stimulation of the reticuloendothelial system. The intramuscular and intravenous routes are to be preferred because of the more generalized distribution into the ocular tissues, the stimulation of the defense mechanism of the entire body and the absence of the inflammatory reaction which usually follows its local use. F. P. GUIDA.

Physiology

THE ORIGIN OF ABNORMAL RETINAL CORRESPONDENCE. T. A'B. TRAVERS, Brit. J. Ophth. **24:** 58 (Feb.) 1940.

The author first recapitulates the findings published in a previous paper (*Brit. J. Ophth.* **22:** 577, 1938) and concludes the present paper with the following summary:

"1. In the normal binocular field there are two visual lines which meet upon the fixation object. This arrangement permits binocular fixation with little or no suppression.

"2. In squint there are two visual lines which do not meet upon the fixation object. This would cause diplopia and confusion unless suppression occurred.

"3. In squint there are two areas of suppression in the binocular field.

"4. There occurs: (*a*) Suppression of the diplopia image. (*b*) Suppression of the part of the field which has the same local sign as the fixing macula. This suppression prevents confusion.

"5. Suppression of the area described in 4 (*a*) is not related to retinal correspondence.

"6. Suppression of the area described in 4 (*b*) is intimately associated with retinal correspondence. It is directly associated with the angle of anomaly, in that the larger the angle of anomaly, the greater the area of suppression.

"7. It has been shown clinically that an abnormal correspondence changes after operation and the angle of anomaly lessens, so does the area of suppression become smaller. When the angle of anomaly becomes 0, and correspondence is normal, there is no suppression.

"8. It is suggested that the first step in the development of abnormal correspondence is macular suppression. Macular suppression in one eye (or part of the binocular field) alters the power of discriminating direction in the deviated component of the binocular field. This allows the normal perception of direction to develop." W. ZENTMAYER.

THE FUNCTION OF VITAMIN A IN THE MECHANISM OF VISION. M. SIMONELLI, Arch. di ottal. **45:** 227 (Sept.-Oct.) 1938.

Simonelli presents a review of the literature on the function of vitamin A in the mechanism of vision. He subscribes to the theories set forth by Wald in his conception of the relation between visual purple and vitamin A.

Simonelli feels that a measurement of the vitamin A level can be accomplished by means of light adaptation tests. He proposes routine light adaptation tests, especially for children, as a test of the adequacy of their dietary habits. F. P. GUIDA.

Retina and Optic Nerve

COMPRESSION OF THE INTRACRANIAL PORTION OF THE OPTIC NERVE. P. DESVIGNES, Arch. d'opht. **2:** 415 (May) 1938.

In this paper Desvignes calls attention to the great importance of a unilateral central scotoma as a localizing sign of a lesion of the optic nerve. A complete examination alone will differentiate the cause of the compression, although very often this is difficult. He describes three clinical syndromes: meningioma of the nasal wing of the sphenoid, olfactory meningioma and suprasellar meningioma. The differential diagnosis is outlined. S. B. WARTON.

HISTOLOGIC STUDY IN A CASE OF BILATERAL SENILE PSEUDOTUMOR OF THE MACULA. Y. L. SANDOZ, Arch. f. Ophth. **140:** 725, 1939.

A brief abstract of the paper under review was presented by Vogt at the annual meeting of the Swiss Ophthalmological Society in 1935. The disease for which Vogt and his school use the term senile pseudotumor of the macula is generally considered to belong to the group of senile disciform degeneration of the macula (Kuhnt-Junius). "To put the senile pseudotumor of the macula in the same group with the various senile degenerations of the macula is a mistake and a source of confusion. To us it seems important to separate clearly the senile pseudotumor of the macula from the flat (not tumor-shaped) degeneration." The clinical findings in the case under review were typical. In a woman 66 years of age first a fine pigmentation of the macula and a central scotoma developed. Later the picture changed to that of a cystic degeneration of the macula; then for several years deeply seated

hemorrhages occurred, became absorbed and recurred. During this period a yellowish prominent mass developed in both maculas. The patient died from cardiac failure, and her eyes became available for histologic examination. The pseudotumor consisted of a mass which looked like hyalin or amyloid but did not give the histochemical reactions characteristic of these substances. A few cells of the fibroblast type were enclosed in the mass. In each eye there was a small rupture of the lamina vitrea through which granulation tissue that had arisen from the choroid was growing into the pseudotumor. There was evidence of arteriosclerosis in the deeper layers of the choroid. The retina had been pushed forward by the mass, and its outer layers had disappeared or degenerated. The pathogenesis of the disease, according to the author, is that of a primary vascular disturbances in the choroid which is followed by reactive processes that lead to the development of a granulation tissue. This perforates the lamina vitrea and gives rise to the hemorrhages and the pseudotumor underneath the retina.

P. C. KRONFELD.

HEREDITY OF FAMILIAL ATROPHY OF THE OPTIC NERVE (LEBER'S DISEASE): REPORT OF A GENEALOGY. P. CIBIS, Klin. Monatsbl. f. Augenh. **102:** 824 (June) 1939.

In a family with 108 members, comprising six generations, Leber's disease occurred positively in 4 persons and evidently in a fifth. These persons, 2 women and 3 men, were descendants of the same ancestor. The disease passed from one male to another and then to female descendants only. This fact is contradictory to Lossen's rule, that a male cannot pass the disease on to a male descendant. The disease was discovered in Cibis' male patients between the ages of 20 and 26 years. The validity of this rule was doubted by Reich and denied by Levit. Cibis agrees with Reich for reasons stated. Another interesting feature was that the disease became manifest in the 2 girls at the age of 6 years. Takahashi found the twentieth year of life the average age in all the cases of Leber's disease in Germany, which he compiled in 1926. The disease appeared between the ages of 12 and 51 in the cases compiled by Kawakami. A predisposing age for the onset of the disease does not exist; this point was observed also by Blegvad and Rönne.

K. L. STOLL.

SPONTANEOUS FORMATION OF A HOLE IN THE MACULA IN CHOKED DISK: REPORT OF A CASE. F. HOLLWICH, Klin. Monatsbl. f. Augenh. **102:** 849 (June) 1939.

Hollwich describes the case of a man aged 19 with a rapidly growing tumor of the epiphysis. Complete choked disk measuring 5 D. was present in the right eye and measuring 7 D. in the left eye. The macula in the right eye showed streaky white degenerative lines. In the macula of the left eye a round hole was observed and photographed, at the edge of which fine, bright cystoid degenerative foci were noted. The paramacular tissue showed radial striation. Vision was reduced to 5/30, and a central scotoma for colors existed. The peripheral outline

of the field of vision was normal. Hollwich explains the formation of the hole in the macula as the joint result of edema, cystoid degeneration and a pull on the foveal layers of the retina caused by forcible and rapid propulsion of the disk.

K. L. STOLL.

Tumors

CLINICAL AND HISTOLOGIC OBSERVATIONS ON ORBITAL TUMORS. E. SCHRECK, Klin. Monatsbl. f. Augenh. **103**: 1 (July) 1939.

Schreck discusses the types and the frequency of orbital tumors which present the clinical symptom "protrusion of the eyeball." He undertook to distinguish the type of tumors by certain clinical symptoms. He examined 259 patients who attended the eye clinic of the University of Heidelberg between 1900 and 1937. Of these, 190 patients were operated on, and they form the first group. The second group comprises the patients not operated on. From these two groups with primary tumors the author separates the third group, with secondary tumors which extended into the orbit from its surroundings. Schreck found that not the group with orbital sarcomas but the one with orbital meningiomas is the largest, including the orbital psammomeningioma. This is followed by the orbital neuroepithelioma and then the neuroblastoma of the fibroblastic and the epithelial type; the latter contains the "rosettes." The so-called mixed tumors of the tear gland are branchiogenous carcinomas of the orbit, which may be traced to fissural exclusions or transportations of cells of the primitive fissures of the gills. A similar origin is attributed to the atheromas and dermoids, which are epidermoid cysts. The frequency of the secondary tumors operated on was in the following order: those arising from the nasal adnexa, the palpebral carcinomas, melanosarcomas (or melanocytoblastomas) of the choroid, nevus carcinomas of the conjunctiva, neuroepitheliomas of the retina and lastly, metastases of the mamma and genitals. The patients not operated on had pseudotumors, such as syphilomas, tuberculomas, tumors of the hypophysis and metastases. Although his attempt to gain some data for an early diagnosis of the divers types of tumors failed, Schreck was successful in gaining knowledge of certain characteristics of tumors. The paper is well illustrated with numerous photomicrographs and tables.

K. L. STOLL.

CANCER OF THE MEIBOMIAN GLANDS. S. SKRIPTCHENKO, Vestnik oftal. **8**: 93, 1939.

The patient, aged 68, had a "stye" of the left lower lid three years previously which began to grow slowly until it reached the size of a hazelnut, with ulceration of the margin of the lid. The tumor measured 4 by 5 cm. and was situated deep in the lid. A few firm nodules could be palpated through the intact skin. The free margin of the lid presented a granulating surface with purulent discharge, and the conjunctiva was infiltrated. The lid was removed and covered by a flap from the cheek. The histopathologic observations are given.

Skriptchenko makes a plea that chalazions should be examined histologically in patients over 40 years old, because carcinoma of the meibomian glands might be mistaken for a chalazion.

This is the fortieth case of cancer of the meibomian glands reported in the world's literature. O. SITCHEVSKA.

Vision

SUBJECTIVE STUDY OF VISUAL ABERRATIONS. E. JACKSON, Am. J. Ophth. **22:** 384 (April) 1939.

This interesting article does not lend itself to abstracting. It deals with subjective visual sensations and is a plea for careful study of these phenomena in the borderland between vision, neurology and philosophy, since there is a tendency for examination of patients to become habitual, routine and unproductive. W. S. REESE.

Therapeutics

THERMAL REACTION OF THE HEALTHY AND OF THE DISEASED RABBIT'S EYE TO VARIOUS THERAPEUTIC METHODS. R. SCHMIDT, Klin. Monatsbl. f. Augenh. **102:** 788 (June) 1939.

The author renders a short résumé of the development of thermotherapy and describes his methods in applying dry heat, moist heat, short wave treatment and massage. His results on healthy and on diseased eyes of rabbits are reported. The healthy eyes could be influenced in a high measure by dry and moist heat and short wave irradiation; yielded less or partial or no result was obtained by other methods, e. g. subconjunctival injections of saline solution or application of a 5 per cent ethylmorphine hydrochloride ointment or of yellow mercuric oxide salve. The temperature of the diseased eye ranged about 2 degrees higher than that of the normal eye. Heating pads and short wave irradiation yielded about the same rise of temperature in healthy and in slightly inflamed eyes. In severe inflammations, however, the temperature of the cornea and of the anterior chamber showed an increase of 1.2 degrees and that of the vitreous rose 0.6 degrees after the treatment. The result of heat treatment is limited by regulatory processes in the eye in eliminating excess heat by way of the blood circulation. Only a certain temperature can be obtained, which may drop even after application of additional heat. Normal temperatures were observed a few minutes after the treatments. K. L. STOLL.

Society Transactions

EDITED BY W. L. BENEDICT

DETROIT OPHTHALMOLOGICAL SOCIETY

PARKER HEATH, M.D., *President*

EDMOND L. COOPER, M.D., *Recorder*

Nov. 28, 1940

Some Practical Considerations in Refraction. DR. ALFRED COWAN, Philadelphia.

A cycloplegic should be used for refraction in every case unless there is some contraindication or unless the patient's power of accommodation is so low that it can be considered negligible. The inconvenience to the patient of temporary cycloplegia is not a serious objection, and glaucoma resulting from the use of a cycloplegic is an extremely rare occurrence provided a careful preliminary examination is made.

It is a mistake to say that presbyopia begins at any certain age, since its onset depends on the standards for distinct vision and on the kind of work done by the individual person. A person may be presbyopic and still have some power of accommodation, and a full correction for distance vision often may enable a hyperopic person 45 or 46 years of age to postpone for a time the wearing of bifocal lenses.

Homatropine hydrobromide is the cycloplegic of choice except for younger children, for whom atropine sulfate is more efficient. One should choose the drug that will cause the least inconvenience and at the same time answer the purpose. The results of retinoscopic examination alone should not be depended on unless the patient cannot be examined subjectively. The most accurate method for determination of the refraction of the eye is still the method of Donders, by which the error of refraction is found by use of that lens which produces the best visual acuity.

A postcycloplegic test should be done in every case. The purpose of this test is not to measure the exact static refraction, since this was done during cycloplegia, but to determine just how much of the static refraction must be corrected. The postcycloplegic test is begun with both eyes open and with the patient wearing the full static correction. The power and axis of a cylinder are not changed on the postcycloplegic examination, this test being really only a method of fogging. Equal additions to or subtractions from the spherical correction should be placed before the two eyes at the same time. The exact difference in the refraction between the two eyes always should be maintained in the correcting lenses. The final prescription will depend on the ophthalmologist's experience and judgment with regard to the history and symptoms, on the age and occupation of the patient and on whether or not the patient has previously worn glasses.

Emmetropia is not the ideal state of ocular refraction that the definition would indicate. If in a young person with normal accommodation one finds emmetropia during complete cycloplegia, the tone of the accommodation alone, when it returns, will produce myopia of from 0.25 to 1 D. Therefore, actual emmetropia in a young person requires that some degree of hyperopia be found during cycloplegia. Clinically, no one standard can be set up for the ideal eye. In an infant, about 4 D. of hyperopia is probably desirable, while 1 D. of hyperopia in a person 50 years of age is a material refractive error and requires full correction. Exact emmetropia is desirable after maturity, but in a young child it is a potentially serious condition.

The old rule of Donders that in cases of hyperopia one must beware of giving too weak glasses and in cases of myopia of giving too strong glasses has long been disregarded by me. Ordinarily, for young persons (except when there is evidence of strabismus) I do not deem it advisable to order glasses for moderate degrees of hyperopia, provided the error is the same in both eyes. In cases of strabismus, however, it is best to correct the whole or nearly the whole static error.

A difference in refraction of the two eyes, even when small, may be an important cause of asthenopia, and I am convinced that a most careful correction should be given in cases of anisometropia.

The management of myopia depends on whether one is dealing with a simple refractive error or with a disease of the eye. Simple myopia with no evidence of disease is no more serious a condition than hyperopia or astigmatism, except that it naturally increases during the growing age. Nothing one can do will arrest this natural progress. Neither accommodation nor convergence has ever been shown to cause simple myopia, and wearing proper glasses has never been shown to arrest its progress. Full correction should be given for myopia, since it gives the best visual acuity, and examinations should be made at short intervals to keep up with changes in the refraction of the eye.

Malignant myopia is different, and I have never seen simple myopia turn into malignant myopia. Every attempt should be made to detect the slightest signs of low grade uveitis in every myopic child. If this is present the ophthalmologist is required to treat a disease, not an ametropia. He should treat it as he sees fit, but he should remember that he cannot cure it with concave glasses.

DISCUSSION

[NOTE: The discussion was in the form of written questions.]

QUESTION: How often do you find it necessary to prescribe contact glasses?

DR. ALFRED COWAN: They are very disappointing in cases of simple ametropia, and the patients soon give them up. In cases of conical cornea and in some cases of aphakia they are the only means of affording good visual acuity, and the results are better.

QUESTION: What is your opinion with regard to the wearing of prisms in cases of esophoria?

DR. ALFRED COWAN: I never prescribe prisms for constant use in cases of esophoria.

QUESTION: Are not most commercially produced test charts illuminated with 7 foot candles? Do you advise stepping up this illumination?

DR. ALFRED COWAN: An illumination of 80 to 100 foot candles should be used in all reading charts, cabinets and projection screens. It is better to keep the rest of the room fairly well lighted, so as to prevent glare from the illuminated chart.

QUESTION: What is the earliest age at which you attempt to correct alternating squint?

DR. ALFRED COWAN: Correction of alternating squint should be begun as early as possible in every case.

QUESTION: What is your opinion of tinted lenses for constant use?

DR. ALFRED COWAN: Tinted lenses for constant use are unnecessary. Any tint which can be worn constantly is not dark enough to have any practical value. In pathologic conditions in which a tinted lens is indicated or for part time wear against unaccustomed glare, a tinted lens may be prescribed, and for these I usually recommend a No. 3 London smoke.

PARKER HEATH, M.D., *President*

EDMOND L. COOPER, M.D., *Recorder*

Dec. 12, 1940

The Lens in Cases of Secondary Glaucoma. DR. PARKER HEATH.

This article will be published in full, with discussion, in a later issue of the ARCHIVES.

Surgery of the Lacrimal Sac. DR. E. L. WHITNEY.

A moving picture in color illustrating the Mosher-Toti and the Dupuy-Dutemps operation was presented. The important features in the success of these two procedures are: (1) a sufficiently large bony opening, made possible by removing a considerable portion of the posterior border of the ascending process of the superior maxilla; (2) extension of the bony opening well above the level of the canaliculi and down into the nasolacrimal duct; (3) preservation of the posterior lacrimal crest, and (4) avoidance of operation in the presence of acute or subacute infection of the lacrimal sac or a paranasal sinus.

No complications have arisen when these principles have been followed. The author's results have followed closely those of the originators of these operations, namely, with the Toti-Mosher procedure 75 per cent of cures were obtained, and with the Dupuy-Dutemps operation, between 90 and 100 per cent, in a total of 125 operative cases. The latter operation is much more tedious to perform, but the anastomosis of the mucous membranes of the sac and the nose is much more likely to maintain a permanent opening into the nose.

DISCUSSION

DR. GORDON WITTER, Port Huron, Mich.: I should like to ask Dr. Whitney whether results are equally good in patients with definite

chronic infection of the sac and in patients with obstruction but with no infection. How long should one wait after an acute attack of dacrocystitis before attempting operation?

DR. E. L. WHITNEY: The best results are obtained in those patients with a mucocele. The least satisfied patients are those with just epiphora. One should not attempt a Toti-Mosher or a Dupuy-Dutemps operation without a wait of at least six weeks after an acute attack.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

ALGERNON REESE, M.D., *Chairman*

BRITTAIN PAYNE, M.D., *Secretary*

Nov. 18, 1940

Anatomy of the Orbit. DR. RAYNOLD N. BERKE (by invitation).

(Pictures of actual anatomic specimens of the orbit were presented to illustrate practical points of clinical and surgical ophthalmology. The osteology of the orbit was reviewed and illustrated by lantern slides, with special emphasis on the bony landmarks of surgical significance. The importance of the supraorbital and infraorbital foramens, the anterior and posterior lacrimal crests, the ethmoid sinuses and the nasolacrimal ducts was emphasized. Colored slides were shown to demonstrate the relation of Horner's muscle and the medial canthal ligament to the lacrimal sac, the relation of the levator muscle to the anatomic structure of the eyelids and the position of the ciliary ganglion with reference to the lateral rectus muscle and the optic nerve. Other practical points were illustrated by three-dimensional dissections of the orbit.)

The Central Nervous System, with Particular Regard to the Visual Pathway and the Oculomotor System. DR. GEORGE A. BLAKESLEE.

(The visual apparatus was demonstrated, with its connections in the primary visual centers, and then followed to its termination in the occipital lobes. Lesions along its course, due to tumors of the brain, vascular diseases, acute infections, toxic agents and degenerative diseases with resultant symptoms and signs, were discussed. The anatomic and histologic character of the motor oculi nerve was shown, and the symptoms and signs of diseases affecting the intrinsic and extrinsic ocular muscles were described.)

Anatomy of the Eyeball. DR. BRUCE FRALICK (by invitation).

(Practical applications of known anatomic relations were described and illustrated to point out certain avoidable mistakes in ophthalmic surgical technic. Several operations on the globe were discussed. Variations in the usual technic were suggested after careful consideration of the anatomic factors involved.)

ALGERNON REESE, M.D., *Chairman*

BRITTAIN PAYNE, M.D., *Secretary*

Dec. 16, 1940

Intraepithelial Epitheliomas of the Cornea. DR. JOHN S. MCGAVIC (by invitation).

A patient with trachoma grade III had been successfully treated with sulfanilamide except for a fleshy pannus remaining on one cornea. This was removed surgically, Bowman's membrane being left intact. Microscopically the lesion was an intraepithelial epithelioma identical with the lesions of Bowen's disease of the skin and mucous membranes. (Three similar cases were reviewed.) The tumor appeared as a diffuse, reddish gray, flat, highly vascularized lesion which did not invade or metastasize as early as does the usual epithelioma. The prognosis and treatment were discussed.

Lattice Keratitis: Report of a Case. DR. W. GUERNSEY FREY JR.

A white man aged 50 complained of failing vision, pain and photophobia of both eyes, with recurrent attacks for three years. Corneal lesions were present, consisting of fine gray coalescing spots with branching and interlacing lines. Blood transfusions gave temporary relief, but the keratitis continued to progress.

Symmetric Bilateral Colobomas of the Iris, Ciliary Body, Retina and Choroid: Report of a Case. DR. MARTIN H. KILMANN (by invitation).

Examination of a youth aged 17 revealed symmetric bilateral colobomas of the iris, ciliary body, lens, retina and choroid. The colobomas were typical and were associated with microphthalmia. Vision of 20/30 was maintained in each eye.

A New Technic of Operation for Pterygium: Report of a Case in Which the Procedure Was a Success. DR. WILLIAM B. DOHERTY.

The operation consists of the use of fixation forceps and a silk suture to transfix the pterygium, by which it is separated from the cornea with a sawing motion. The pterygium is passed under a conjunctival pocket above, previously prepared, and is fixed with sutures. The conjunctival edges are approximated and sutured.

Episcleritis Associated with Rheumatoid Arthritis: Report of Three Cases. DR. JULES W. SMOLEROFF (by invitation).

Malignant Teratoma of the Orbit: Report of a Case. DR. ALBERT V. SARADARIAN (by invitation).

Boeck's Sarcoid: Report of a Case. DR. JESSE M. LEVITT (by invitation).

Capsulotomy and Iridocapsulotomy Technic with a Special Keratome and Iridocapsulotomy Scissors. DR. CONRAD BERENS.

To avoid serious complications from operation, all but the finest capsular membranes should be cut with scissors because of the great danger of traction on the ciliary body with resulting iridocyclitis. A sharp, hollow ground, narrow keratome is used to penetrate the sclera subconjunctivally and to perforate the iris and capsule. The incision in the iris and capsule is made with iridocapsulotomy scissors (modified Noyes), which fill the scleral opening and are easy to manipulate. The position of the incision varies according to the condition which is present.

The Mechanics of Optic Nerve Traction on the Retina During Ocular Rotation, with Special Reference to Retinal Detachment. DR. BENJAMIN FRIEDMAN.

This article will be published in full in a later issue of the ARCHIVES.

Book Reviews

Die Pathologie der optischen Nachbilder und ihre klinische Verwertung. By Dozent Dr. Vladimir Vujić and Dr. Kurt Levi. Paper. Price 8 Swiss francs. Pp. 86. Basel: S. Karger, 1939.

Studies of optical after-images, intensively pursued, have added to knowledge of the physiology and psychology of vision and its associated functions. They were used in testing the field of fixation, by Hering; for determination of the primary position of the visual axes, by Helmholtz; in research concerned with normal vision, by Wheatstone, Rogers, Wundt and Volkmann, and in ascertaining complementary relations in normal color sensation. From the pathologic standpoint, however, little has been done, and as to pathologic manifestations of after-images themselves practically nothing is known.

With this in mind, the authors have used the material of the neurologic clinic of the University of Belgrade, Yugoslavia, and have examined a large number of patients, about 200 in all. In all but a small minority of cases they found anomalies of the after-images, ranging from tabes, multiple sclerosis, epilepsy, cranial traumatism, tumor and abscess of the brain, cerebral syphilis and chronic encephalitis to migraine, chronic alcoholism, lead poisoning, morphinism, hyperthyroidism and various psychoses. Deviations from the norm were presented as more or less complete absence of after-images in one or both eyes and/or as anomalies of form, intensity, duration, latency and size, with bizarre aberrations in a number of cases. The authors note the early appearance of these anomalies, which is significant and of practical importance in diagnosis, prognosis and therapy.

PERCY FRIDENBERG.

A Treatise on Medicolegal Ophthalmology. By Albert C. Snell, M.D., Rochester, N. Y. Price, $6. Pp. 312, illustrated. St. Louis: C. V. Mosby Company, 1940.

The aim of this book, as presented in a well defined introduction, is to call attention to the scientific importance of medical jurisprudence, a subject not taught at present in medical schools. It also presents a much needed method by which in most legal cases, according to the author, the amount of loss of vision may be accurately determined on a percentage basis.

In the first chapters the author ably discusses the duties and rights of a medical witness and the physician's privileges as to professional secrecy and gives valuable information as to how the physician may avoid suits for malpractice.

This is followed by a brief history of the compensation laws in Europe as well as in the United States, with special reference to the state and federal laws relating to injuries of the eye. Various methods for evaluating visual disabilities which have been proposed in Europe and in the United States are also comprehensively discussed.

The functions essential to a useful eye are visual acuity, resolving power, peripheral vision and muscle function. Therefore, a mathematical

formula must be found which will serve as a basis for computing the visual efficiency as a whole when one or more of these functions is subnormal. Several chapters are devoted to this important subject, in which all steps in the process of evolving a standard method for evaluating degrees of visual disability are treated in detail. The author advocates the acceptance and general use of the method recommended by the Section on Ophthalmology of the American Medical Association.

In the final chapters he gives advice demonstrating the proper examination of patients and the practical application of this medicolegal method when the human element must be taken into consideration.

One important chapter deals entirely with malingering. The author elucidates its many sinister aspects and the means by which it may be detected.

The book is well written, in an easy, flowing style, and contains a wealth of information not generally known. It is therefore a valuable addition to the library of any ophthalmologist. The print is clear and, like the subject matter, easily readable.

ERVIN TÖRÖK.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 33 Welbeck St., London, W., England.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen, Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. H. G. Ditroi, Szeged.
Assistant Secretary: Dr. Stephen de Grosz, University Eye Hospital, Maria ucca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the Secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.

PALESTINE OPHTHALMOLOGICAL SOCIETY

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

POLISH OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Dr. Malcolm Hepburn, 111 Harley St., London, W. 1, England.
Secretary: Dr. C. Dee Shapland, 15 Devonshire Pl., London, W. 1, England.

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Francisco Ferreira, Pitangueiras 15, Brotas, S. Salvador, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Albert C. Snell, 53 S. Fitzhugh St., Rochester, N. Y.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, SECTION ON OPHTHALMOLOGY

President: Dr. Frank E. Brawley, 30 N. Michigan Ave., Chicago.
Executive Secretary-Treasurer: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha.

AMERICAN OPHTHALMOLOGICAL SOCIETY

President: Dr. F. P. Calhoun, 478 Peachtree St. N. E., Atlanta, Ga.
Secretary-Treasurer: Dr. Eugene M. Blake, 303 Whitney Ave., New Haven, Conn.
Place: Hot Springs, Va. Time: May 29-31, 1941.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

Chairman: Dr. John Evans, 23 Schermerhorn St., Brooklyn.
Secretary-Treasurer: Dr. C. S. O'Brien, University Hospital, Iowa City.

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

CANADIAN OPHTHALMOLOGICAL SOCIETY

President: Dr. J. Vaillancourt, 46 St. Louis St., Quebec.
Secretary-Treasurer: Dr. Alexander E. MacDonald, 421 Medical Arts Bldg., Toronto.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President-Emeritus: Mr. William Fellowes Morgan, 50 W. 50th St., New York.
Secretary: Miss Regina E. Schneider, 50 W. 50th St., New York.
Executive Director: Mrs. Eleanor Brown Merrill, 50 W. 50th St., New York.

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. V. May, 1703 Main St., Marinette.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.
Place: Wisconsin Rapids. Time: June 1941.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. William D. Rowland, 84 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Trygve Gundersen, 243 Charles St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. Isaac H. Jones, 635 S. Westlake Ave., Los Angeles, Calif.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Clarence W. Shannon, 4th and Pike Bldg., Seattle.
Secretary-Treasurer: Dr. Purman Dorman, 1215–4th Ave., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month, except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. W. E. Rideout, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. J. J. Potter, 303 N. Main St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. M. Kessler, 311 Center Ave., Bay City, Mich.
Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Davis, 1615 Howard St., Omaha.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. Grady E. Clay, Medical Arts Bldg., Atlanta, Ga.
Secretary: Dr. John R. Hume, 921 Canal St., New Orleans.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. Franklin P. Maury, Professional Bldg., Tucson, Ariz.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. J. K. Heckert, 103 N. Washington St., Lansing.
Secretary-Treasurer: Dr. W. D. Irwin, 710 Hanselman Bldg., Kalamazoo.
Time: Third Thursday of alternate months.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. C. H. Bailey, 29 S. Oakland Ave., Sharon.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. R. R. Kirkpatrick, 6th and Walnut Sts., Texarkana, Ark.
Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. W. E. McClellan, 750 Main St., Hartford.
Secretary-Treasurer: Dr. S. J. Silverberg, 201 Park St., New Haven.

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.
Place: Macon. Time: May 13-17, 1941.

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. J. K. Von Lackum, 117–3d St. S.E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President: Dr. Roy Grigg, Bozeman.
Secretary: Dr. A. W. Morse, 507 Phoenix Bldg., Butte.

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY, OTOLOGY AND RHINOLARYNGOLOGY

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.
Place: Atlantic City. Time: June 3-5, 1941.

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. N. A. Youngs, 322 De Mers Ave., Grand Forks.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. E. W. Carpenter, 200 E. North St., Greenville.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.
Place: San Antonio. Time: December 1941.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Rowland H. Merrill, 1010 First National Bank Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 628 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. George G. Hawkins, Newport News.
Secretary-Treasurer: Dr. Guy Fisher, 3 E. Beverley St., Staunton.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Black, 7 W. Bowery St., Akron, Ohio.
Secretary-Treasurer: Dr. C. R. Andersen, 106 S. Main St., Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Maurice Wieselthier, 1322 Union St., Brooklyn.
Secretary-Treasurer: Dr. Harold F. Schilback, 142 Joralemon St., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. James G. Fowler, 412 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Richard Gamble, 30 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati Ophthalmic Club

Chairman: Each member, in rotation.
Secretary-Treasurer: Dr. E. R. Thomas, 819 Carew Tower, Cincinnati.
Place: Holmes Memorial Library, Cincinnati General Hospital. Time: 8:15 p. m., third Monday of each month except June, July and August.

Cleveland Ophthalmologic Club

Chairman: Dr. Albert D. Ruedemann, Cleveland Clinic, Cleveland.
Secretary: Dr. B. J. Wolpaw, 2323 Prospect Ave., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. C. D. Postle, 240 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. Hugh C. Thompson, 289 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. Dan Brannin, Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. L. E. Darrough, 4105 Live Oak St., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. L. A. Hulsebosch, 191 Glen St., Glen Falls.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Wallace W. Ralston, 1304 Walker Ave., Houston, Texas.
Secretary: Dr. William J. Snow, 708 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Paul Southgate, 117 E. 8th St., Long Beach, Calif.
Secretary-Treasurer: Dr. Kirt G. Parks, 605 Professional Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. John P. Lordan, 2007 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Colby Hall, 1136 W. 6th St., Los Angeles.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John B. Hitz, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. Leonard C. Whiting, 121 Whitney Ave., New Haven, Conn.
Secretary: Dr. Frederick A. Wies, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Algernon Reese, 73 E. 71st St., New York.
Secretary: Dr. Brittain Payne, 35 E. 70th St., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. Morris Davidson, 80 Centre St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. Howard Heine, 635 N. Main St., Fremont, Neb.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m., dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

Chairman: Dr. Edmund B. Spaeth, 1930 Chestnut St., Philadelphia.
Secretary: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President: Dr. Edward A. Weisser, 119–5th Ave., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.
Place: Rochester Academy of Medicine, 1441 East Ave. Time: 5 p. m., Jan. 22. 1941.

ST. LOUIS OPHTHALMIC SOCIETY

President: Dr. J. F. Hardesty, Missouri Theatre Bldg., St. Louis.
Secretary: Dr. Carl C. Beisbarth, 3720 Washington Blvd., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

SAN ANTONIO OPHTHALMOLO-OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas.
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

SAN FRANCISCO COUNTY MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

SHREVEPORT EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

SPOKANE ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Louis A. Parsell, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. Robert L. Pohl, 407 Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

SYRACUSE EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. F. R. Webster, State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. John R. Myers, State Tower Bldg., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

TOLEDO EYE, EAR, NOSE AND THROAT SOCIETY

Chairman: Dr. S. H. Patterson, 1251–15th St., Toledo, Ohio.
Secretary: Dr. J. E. Minns, 316 Michigan St., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

TORONTO ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

WASHINGTON, D. C., OPHTHALMOLOGICAL SOCIETY

President: Dr. Frank Costenbader, 1726 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. L. Conner Moss, 1710 Rhode Island Ave. N.W., Washington, D. C.
Place: Episcopal Eye, Ear and Throat Hospital. Time: 7:30 p. m., first Monday in November, January, March and April.

WILKES-BARRE OPHTHALMOLOGICAL SOCIETY

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.